Medtronic

Micro Therapeutics, Inc. d/b/a ev3 Neurovascular, a subsidiary of Medtronic

INSTRUCTIONS FOR USE

Onyx™ Liquid Embolic System (LES)

en TABLE OF CONTENTS

Onyx™ Liquid Embolic System (LES)

English en
Instructions for Use

Onyx™ Liquid Embolic System (LES)

CAUTION
- Federal (USA) law restricts this device to sale by or on the order of a physician.
- This device should be used by physicians with a thorough understanding of angiographic and percutaneous neurointerventional procedures.

DESCRIPTION
Onyx™ Liquid Embolic System (LES) is a non-adhesive liquid embolic agent comprised of EVOH (ethylene vinyl alcohol) copolymer dissolved in DMSO (dimethyl sulfoxide) and suspended micronized tantalum powder to provide contrast for visualization under fluoroscopy. The Onyx™ LES consists of a 1.5 mL vial of the Onyx™ LES, a 1.5 mL vial of DMSO, two 1 mL Onyx™ LES delivery syringes, and one 1 mL DMSO syringe. An Onyx™ LES/DMSO compatible delivery microcatheter that is indicated for use in the neurovasculature is used to access the embolization site. An optional syringe adapter may be used if available for the associated microcatheter. Onyx™ LES is available in two product formulations, Onyx™ LES 18 (6% EVOH) and Onyx™ LES 34 (8% EVOH).

Onyx™ LES 18 (nominal viscosity of 18 cSt at 40 °C) is expected to travel more distally and penetrate deeper into the nidus for a brain arteriovenous malformation (bAVM) or middle meningeal artery for subdural hematoma due to its lower viscosity compared to the Onyx™ LES 34 (nominal viscosity of 33 cSt at 40 °C). Final solidification occurs within five minutes for both product formulations.

DEVICE COMPATIBILITY
An Onyx™ LES/DMSO compatible delivery microcatheter that is indicated for use in the neurovasculature is used to access the embolization site. An optional syringe adapter may be used if available for the associated microcatheter. Refer to labeling provided with other medical technologies to determine compatibility.

PRINCIPLE OF OPERATION
The Onyx™ LES is delivered by slow controlled injection through a microcatheter into the brain arteriovenous malformation or middle meningeal artery (MMA) target branch/es under fluoroscopic control. The DMSO solvent dissipates into the blood, causing the EVOH copolymer and suspended tantalum to precipitate in situ into a spongy, coherent embolus. The Onyx™ LES immediately forms a skin as the polymeric embolus solidifies from the outside to the inside, while traveling more distally in the lesion.

INTENDED USE / INDICATIONS FOR USE
1. Onyx™ LES is indicated for presurgical embolization of brain arteriovenous malformations (bAVMs).
2. Onyx™ LES is indicated for embolization of the middle meningeal artery (MMA) as an adjunct to surgery for the treatment of symptomatic subacute or chronic subdural hematoma (SDH).

CONTRAINDICATIONS
The use of the Onyx™ LES is contraindicated when any of the following conditions exist:
- When optimal catheter placement is not possible.
- When provocative testing indicates intolerance to the occlusion procedure.
- When vasospasm stops blood flow.

DIRECTIONS FOR USE

WARNING
- Verify that adequate sedation is used throughout the embolization procedure. Insufficient sedation may result in patient discomfort or movement. Patient movement during embolic agent injection may result in embolization of an unintended vessel.

NOTE: Adjunctive coil use should be considered if angiography shows that venous drainage of the bAVM appears almost simultaneously with arterial opacification.

Major pre-preparation procedures:
- General anesthesia or conscious sedation with monitored anesthesia care (MAC) performed per institutional procedure.
- Prepare pressurized bag(s) of heparinized saline/saline per institutional procedure.
- Selection of sheath, guide catheter/microcatheter and guidewire(s) by operator familiarity and preference.
- Connect flushing to access catheter(s) where appropriate with a very slow rate (1 drop every 2 seconds).
- Systemic heparinization per institutional procedure.

1. Refer to warnings, precautions, potential complications, storage and disposal, and adverse events prior to use.
2. Shake the Onyx™ LES at least 20 minutes on an Onyx™ LES mixer[1] at a setting of 8.

WARNING
- Failure to continuously mix the Onyx™ LES for the required time (20 minutes) may result in inadequate suspension of the tantalum, resulting in inadequate fluoroscopic visualization during delivery.

3. Continue mixing until ready to inject the Onyx™ LES into 1 mL luer-lock delivery syringe per step 10.
4. Confirm DMSO-compatible microcatheter placement into target site with injection of contrast agent per institutional procedure. Establish appropriate working projection that shows the microcatheter tip.

WARNING
- Use only Onyx™ LES/DMSO compatible microcatheters indicated for use in the neurovasculature and syringes. Other microcatheters or syringes may not be compatible with DMSO and their use can result in thromboembolic events due to catheter degradation.

5. Flush contrast from microcatheter with heparinized saline/ saline and leave the syringe connected.
6. Aspirate DMSO into the yellow 1 mL luer-lock delivery syringe for DMSO.
7. Attach the DMSO syringe directly into the hub of the DMSO compatible microcatheter.
8. Inject sufficient volume of DMSO to match microcatheter dead space. Refer to delivery catheter labeling for dead space volume.

WARNING
- Use only 1 mL syringe to inject DMSO and the Onyx™ LES. Other syringes may not be compatible with DMSO.

9. Ensure that Onyx™ LES has been continuously mixed for the required time per step 2.
10. Wipe the Onyx™ LES vial top with an alcohol pad and fill the white syringe with the Onyx™ LES through an 18 or 20 gauge needle.
11. Once DMSO has been injected into catheter dead space, remove the DMSO syringe.
12. Hold catheter hub in a vertical position and overfill and wash hub with balance of DMSO.
13. While holding the Onyx™ LES syringe in a vertical position, immediately connect the microcatheter hub to the Onyx™ LES syringe, make sure there is no air in hub during connection.
14. For optimal fluoroscopic visualization, continue to hold the Onyx™ LES syringe vertically and begin injecting Onyx™ LES to displace DMSO.
15. Continue holding syringe vertically until Onyx™ LES passes through catheter hub.
16. Use only thumb pressure to inject Onyx™ LES at a slow, steady recommended rate of 0.16 mL/minute. Do not exceed specified maximum rate of 0.3 mL/ minute per IFU instructions.
17. Once Onyx™ LES passes through hub, hold syringe in comfortable position.
18. Monitor volume injected to correspond to volume of vascular space being filled.
19. Upon completion of Onyx™ LES injection, wait a few seconds.
20. Slightly aspirate syringe.
21. Gently pull microcatheter to separate it from Onyx™ LES cast.
22. After the microcatheter is withdrawn from the guide catheter, examine the RHV of the guide catheter for any retained droplets of Onyx™ LES, then aspirate and double flush the guide catheter.
23. Once the guide catheter is thoroughly inspected and flushed, do a follow-up angiogram.

WARNINGS
- Premature solidification of the Onyx™ LES may occur if microcatheter luer contacts saline, blood or contrast of any amount.
- Inject Onyx™ LES immediately after mixing. If the Onyx™ LES injection is delayed, tantalum settling can occur within the syringe resulting in poor visualization of Onyx™ LES during injection.
- Do not exceed 0.3 mL/minute injection rate. Animal studies have shown that rapid injection of DMSO into the vasculature may lead to vasospasm and/or angionecrosis.
- Only use thumb pressure to inject the Onyx™ LES at the recommended rate of 0.16 mL/minute. Using palm of hand to advance plunger may result in catheter rupture due to over-pressurization in the event of catheter occlusion.
- Adequate fluoroscopic visualization must be maintained during the Onyx™ LES delivery to avoid non-target vessel embolization. If visualization is lost at any time during the embolization procedure, STOP the Onyx™ LES delivery until adequate visualization is re-established.
- Onyx™ LES can lead to increased procedural risk of unintended embolization when encountering an anatomic variation (e.g., ophthalmic collateral).
- Do not allow more than 1 cm of the Onyx™ LES to reflux back over catheter tip.
- Angioarchitecture, vasospasm, excessive Onyx™ LES reflux, or prolonged injection time may result in difficult catheter removal and potential entrapment.
- Excessive force to remove an entrapped catheter may cause serious intracranial hemorrhage.
- The long-term effects of an entrapped catheter that is left in a patient are unknown, but potentially could include clot formation, infection, or catheter migration.
- After using a microcatheter with the Onyx™ LES, do not attempt to clear or inject any material through it. Such attempts may lead to embolus or embolization of an unintended area.
- STOP injection if the Onyx™ LES is not visualized exiting catheter tip. If the catheter becomes occluded, over-pressurization can occur. During the Onyx™ LES injection, continuously verify that the Onyx™ LES is exiting the catheter tip. Testing has shown that over-pressurization and rupture can occur if 0.05 mL of the Onyx™ LES is injected and is not visualized exiting the catheter tip.

[1]Scientific Industries Genie 2, Model No(s). 120V SI-0240, 240V SI-0251, Vial Attachment No. OA-0570-010.

WARNINGS

- STOP injection if increased resistance to the Onyx™ LES injection is observed. If increased resistance occurs, determine the cause (e.g., the Onyx™ LES occlusion in catheter lumen) and replace the catheter. Do not attempt to clear or overcome resistance by applying increased injection pressure, as use of excessive pressure may result in catheter rupture and embolization of unintended areas.
- DO NOT interrupt the Onyx™ LES injection for longer than two minutes prior to re-injection. Solidification of the Onyx™ LES may occur at the catheter tip resulting in catheter occlusion, and use of excessive pressure to clear the catheter may result in catheter rupture.

Catheter Retrieval Instructions

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

- Angioarchitecture
- Vasospasm
- Reflux
- Injection time

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

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

- Carefully pull the catheter to assess any resistance to removal.
- If resistance is felt, remove any "slack" in the catheter.
- Gently apply traction to the catheter (approximately 3-4 cm of stretch to the catheter).
- 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 catheter is retrieved.

For entrapped catheters:

- Under some difficult clinical situations, rather than risk rupturing the malformation and consequent hemorrhagic complications by applying too much traction on an entrapped catheter, it may be safer to leave the microcatheter in the vascular system.
- This is accomplished by stretching the catheter and cutting the shaft near the entry point of vascular access allowing the catheter to remain in the artery.
- If the catheter breaks during removal, distal migration or coiling of the catheter may occur. Same day surgical resection should be considered to minimize the risk of thrombosis.

ADVERSE EVENTS

- Two prospective, randomized, multi-center clinical trials were conducted on the Onyx™ LES. Refer to CLINICAL STUDY RESULTS - SUBACUTE / CHRONIC SDH section for adverse events reported in the EMBOLISE trial evaluating patients with subacute or chronic SDH. Refer to CLINICAL STUDY RESULTS - BRAIN AVM section for adverse events reported in the Onyx™ LES vs. TRUFILL™ n-BCA trial evaluating patients with brain AVMs.

PATIENT COUNSELING INFORMATION

In accordance with local regulations, healthcare providers should review the Instructions for Use for applicable information to be shared with the patient.

An MRI Card, which contains identifying information about the implanted device, is included in the device package. The MRI Card shall be provided to patients for whom the Onyx™ LES will remain implanted after the procedure.

If the device is implanted, complete the MRI Card and provide it to the patient before they are discharged. Healthcare providers should communicate the following instructions to their patients:

- Always carry their MRI card with them.
- Always inform any healthcare personnel that they have an implanted device before any procedure has begun.
- Contact their healthcare provider if they notice any new or changing symptoms.

NOTE: MRI Card may not be applicable for all regions where it is received.

POTENTIAL COMPLICATIONS

Potential complications of the device and the embolization procedure, include or are synonymous with, but may not be limited to the following:

- Access site complications such as fistula, pseudo-aneurysm, pain and tenderness, inflammation, necrosis, granuloma, pathological hand cold intolerance, amputation, hematoma or hemorrhage, compartment syndrome, hand dysfunction
- Allergic reaction
- Arrhythmia
- Catheter entrapment
- Catheter rupture
- Complications of radiation exposure (e.g. alopecia, burns ranging in severity from skin reddening to ulcers, cataracts, and delayed neoplasia) increases as the procedure time and the number of procedures increase
- Contrast related complications including but not limited to burning sensation, nausea, contrast nephropathy
- Death
- Device migration and cast movement
- Headache
- Infection
- Intracranial hemorrhage or hemorrhage in another vascular location
- Ischemic events: TIA/stroke
- Myocardial infarction
- Nerve damage or cranial nerve palsy
- Neurological deficits/ dysfunctions
- Pulmonary embolism
- Seizures
- Thrombocytopenia
- Thromboembolic events
- Vascular complications including but not limited to dissection, perforation, rupture, occlusion, vasospasm, hypotension
- Visual complications related to anatomical variants (ophthalmic collateral)

*If a serious incident related to the device occurs, contact your Medtronic representative and the competent authority in your respective country/region.

WARNING

- Due to the possibility of electrical arcing with the tantalum metal in the Onyx™ LES material, use of monopolar electrocautery devices for surgical resection of bAVMs embolized with the Onyx™ LES should be avoided. Bipolar devices should be used with caution.

WARNINGS

- This device is supplied STERILE for single use only. Do not reprocess or resterilize. Reprocessing and re-sterilization increases the risks of patient infection and compromises device performance.
- The safety and effectiveness of the Onyx™ LES as a long term implant has not been established.
- Not for use with premature infants (<1500 g) or individuals with significant liver and kidney function impairment.
- Performing embolization to occlude blood vessels is a high-risk procedure. This device should be used only by physicians with neurointerventional training and a thorough knowledge of the pathology to be treated, angiographic techniques, and super-selective embolization.
- After Onyx™ LES embolization of the arteries, feeding bAVM or target branch/es of the MMA may be subject to increased pressures as a result of changes in hemodynamics. Increased arterial pressures could result in hemorrhagic complications.
- Animal experimentation has shown that when the Onyx™ LES escapes outside the vascular space, as might occur if the vessel wall is compromised, a subacute inflammatory response to the material may occur. Increased intracranial pressure due to unresorbed Onyx™ LES material in this space may cause tissue damage.
- DMSO can initiate the liberation of histamine and there has been an occasional hypersensitivity reaction with topical administration of DMSO. This hypersensitivity has been reported in one patient being treated for interstitial cystitis. If anaphylactoid symptoms develop, appropriate therapy should be instituted.

WARNINGS

- DMSO may interact with other embolic agents, such as polymer coated coils, e.g., gel coatings and suture material coated coils.
- Therapeutic embolization should not be performed when high blood flow precludes safe infusion of the embolic agent.
- The microcatheter tip should be placed so that embolization of the bAVM occurs distal to any arterial vessels that may supply normal brain tissue or cranial nerves.
- For additional Materials of Concern information such as REACH, CA Prop 65 or other product stewardship programs, go to www.medtronic.com/productstewardship.
- The safety and effectiveness of this device for radial neurovasculature access in direct comparison to a transfemoral approach has not been demonstrated. The risks and benefits for radial access against a transfemoral approach should be carefully weighed and considered for each patient.

PRECAUTIONS

- The safety and effectiveness have not been studied in the following patient populations:
  - Pregnant and nursing women
  - Individuals less than 18 years old
  - Individuals with aneurysms not associated with a bAVM nidus, or distal feeders to a bAVM nidus
  - Individuals not diagnosed with subacute or chronic subdural hematoma
  - Individuals with significant contraindication to angiography
- Individuals identified with potentially dangerous anatomical variations leading to increased procedural risk. Some data indicate that DMSO potentiates other concomitantly administered medications.
- A garlic-like taste may be noted by the patient with use of the Onyx™ 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 sterile barrier is open or damaged.
- Use the Onyx™ LES prior to the "Use-by date" printed on the package.
- If using radial artery access, perform a screening examination of the radial artery per institutional practices to ensure that radial access is appropriate for the patient.
- If using a guide sheath or introducer sheath, ensure the radial artery lumen diameter is larger than the outer diameter of the guide sheath or introducer sheath.
- Operators should take all necessary precautions to limit X-ray radiation doses to patients and themselves by using sufficient shielding, reducing fluoroscopy times, and modifying X-ray technical factors where possible.
- Verify that the catheters and accessories (see directions for use) used in direct contact with the Onyx™ LES polymer are clean and compatible with the material and do not trigger polymerization or degrade with contact. Use only Onyx™ LES/ DMSO compatible microcatheters indicated for use in the neurovasculature and syringes. Other microcatheters or syringes may not be compatible with DMSO and their use can result in thromboembolic events due to catheter degradation. Refer to the Warnings and Directions for Use sections.
- Wait a few seconds following completion of the Onyx™ LES injection before attempting catheter retrieval. Failure to wait a few seconds to retrieve the microcatheter after the Onyx™ LES injection may result in fragmentation of the Onyx™ LES into non-target vessels.
- To reduce the risk of catheter entrapment, carefully select catheter placement and manage reflux to minimize the following:
  - Angioarchitecture
  - Vasospasm
  - Reflux
  - Injection time
- If catheter entrapment is suspected (with any embolic agent), a fast catheter retrieval technique may result in catheter shaft separation, and potential for

vascular damage, embolism, and thromboembolism. Follow catheter retrieval instructions at the end of the DIRECTIONS FOR USE section.
- If significant traction is required to remove an entrapped catheter, it may be safer to leave the microcatheter in the vasculature.

HOW SUPPLIED

- Onyx™ LES and DMSO are supplied STERILE using dry heat. Onyx™ LES delivery syringes are supplied STERILE using ethylene oxide.
- Onyx™ LES, DMSO and Onyx™ LES delivery syringes are non-pyrogenic.

STORAGE AND DISPOSAL

- This device should be stored in a dry place, away from sunlight.
- Prior to use, maintain product temperature between 19 °C (66.2 °F) and 24 °C (75.2 °F). If product freezes due to exposure to colder temperatures, thaw at room temperature before use.
- Dispose of device in accordance with hospital, administrative, and/or local government policy.

TRAINING

Serious, including fatal, consequences could result with the use of the Onyx™ LES without adequate training. Onyx™ LES implantation should only be performed by physicians who have successfully completed training in the use of Onyx™ LES. Contact your Medtronic sales representative for information on training courses. If any technical assistance is required, contact Medtronic at the telephone number on the back cover of this Instructions for Use.

MR

MAGNETIC RESONANCE IMAGING (MRI) SAFETY INFORMATION

Non-clinical testing demonstrated that the Onyx™ LES is MR Conditional. A patient with this device can be safely scanned in an MR system meeting the following conditions. Failure to follow these conditions may result in injury.

Parameter	Condition of Use / Information
Static Magnetic Field Strength (B0) [T]	≤ 7T
Type of Nuclei	Hydrogen Proton
Static Magnetic Field (B0) Orientation	Horizontal, Cylindrical Bore; Perpendicular to Patient AP; Perpendicular to Patient LR
Maximum Spatial Field Gradient (SFG) [T/m] and [gauss/cm]	30 T/m (3000 gauss/cm)
RF Polarization	Any RF polarization
RF Transmit Coil	Integrated Whole Body Transmit RF Coil; Detachable Head Transmit/Receive Coil; Detachable Extremity Transmit/Receive Coil
RF Receive Coil	Any receive-only RF coil may be used
MR System (RF) Operating Modes or Constraints	First Level Controlled or Normal Operating Mode
Whole Body Averaged SAR [W/kg]	≤ 4 W/kg
Head SAR [W/kg]	≤ 3.2 W/kg
Scan Duration	There is no limit on scan duration for the labeled RF conditions.
Patient Characteristics	Scanning patients who have multiple MR conditional devices present is acceptable as long as the MR labeling conditions for all implants can be satisfied.
MR Image Artifact	The presence of this implant may produce an image artifact.

CLINICAL STUDY RESULTS - SUBACUTE / CHRONIC SDH

Study Purpose

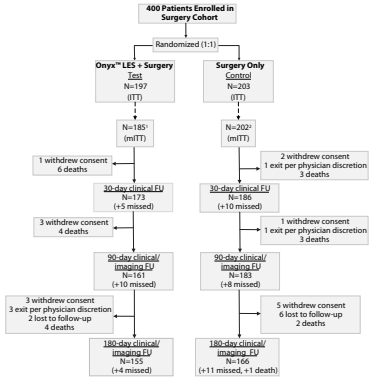
The purpose of the EMBOLISE study (Surgery Cohort) was to evaluate the safety and effectiveness of Onyx™ LES embolization of the MMA as an adjunct to conventional treatment (surgery) for patients with symptomatic subacute or chronic subdural hematoma.

Design

The EMBOLISE study was a multi-center, prospective, randomized, interventional, controlled, open-label, adaptive design IDE clinical trial evaluating the performance of the Onyx™ LES for MMA embolization in patients with symptomatic subacute or chronic SDH. The primary objective was to assess the rate of hematoma recurrence/progression requiring surgical drainage within 90 days post-treatment, OR poor clinical outcome, OR clinical deterioration at 90 days post-treatment.

The study stratified enrollment by patients that were treated with surgery, with and without adjunctive embolization (Surgery Cohort), and those that were treated with medical management, with and without adjunctive embolization (Observational Cohort). Data from the Surgery Cohort of this clinical study provide support for MMA embolization as an adjunct to surgery. A total of 400 patients were enrolled in the Surgery Cohort across 39 sites in the U.S. Patients were randomized on a 1:1 basis to receive either MMA embolization with Onyx™ LES + surgery (test group, 197 patients) or surgery alone (control group, 203 patients). A summary of patient enrollment and completion of clinical follow-up is provided in Figure 1.

Figure 1. Patient Enrollment and Completion of Clinical Follow-Up



ITT population: all patients enrolled in the study who signed the patient informed consent form and were randomized.
mITT population: subset of the ITT population excluding patients who did not successfully complete the treatment to which they were assigned.
[1]From the ITT population, 11 patients were not embolized with Onyx™ LES due to presence of dangerous anatomical variants, and 1 patient withdrew consent prior to receiving any treatment.
[2]From the ITT population, 1 patient did not receive surgery.

Methods

Patients were evaluated for potential enrollment in the Surgery Cohort based on the inclusion and exclusion criteria of the protocol, as described below:

Inclusion Criteria

1. Age ≥ 18 and ≤ 90 years old.
2. Pre-morbid modified Rankin Score (mRS) 0-3.
3. Diagnosis of subacute or chronic SDH by brain imaging (CT or MRI) with corroborating clinical symptoms as specified in the Surgery Cohort.
   a. For SDH to be subacute or chronic, the quantity of acute blood volume must be less than 50%.
4. The patient or patient's LAR has signed and dated an informed consent form (ICF) using the IRB approved ICF and agrees to comply with CIP requirements. HIPAA authorization has been provided and signed by the patient or patient's LAR.
5. Treating neurosurgeon intends to surgically treat subacute or chronic SDH at time of randomization, or patients who can be randomized within 72 hours after surgery has been completed.
6. Patient does not meet criteria for Observation Cohort, e.g.,
   a. Patient with motor deficits 4/5 or worse on Motor Strength Scale (MSS) that is attributable to the location and size of the subacute or chronic SDH at time of randomization OR
   b. Corroborating neurological symptoms due to hematoma beyond minor symptoms (e.g. headache, imbalance, confusion) OR
   c. Midline shift ≥ 5 mm OR
   d. Hematoma thickness > 15 mm.

Exclusion Criteria

1. Life expectancy is less than 1 year.
2. Patient unable to be present or be available for follow-up.
3. Female patient, of child-bearing potential, who is pregnant (confirmed with a positive pregnancy test) or breastfeeding at the time of admission or plans to become pregnant during their participation in the study.
4. Patients diagnosed with acute SDH.
5. Patients identified with potentially dangerous anatomical variations leading to increased procedural risk such as angiographically apparent anastomosis between ophthalmic artery and MMAs (risk of blindness), or patients with access considerations that preclude safe embolization of the MMA.
6. Pre-randomized MGS score ≥ 3.
7. Bleeding disorders or blood diathesis that cannot be controlled or medically managed.
8. Presumed septic embolus, or suspicion of microbial superinfection.
9. Patients with a known active COVID-19 viral infection.
10. CT or MRI evidence of intracranial tumor or mass lesion impinging upon the brain.
11. Significant contraindication to angiography.
    a. Renal failure with serum creatinine > 2.0 mg/dL (or 176 µmol/L) or glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2 and not on dialysis.
    b. History of anaphylactic reaction to imaging contrast.
12. Patient is participating in another clinical trial at any time during the duration of the study that could confound the treatment or outcomes of this investigation.
13. Patient is contraindicated for the use of Onyx™ LES per the investigational device IFU.
14. Patients who cannot be taken off corticosteroids (intended to treat subacute or chronic SDH) for at least 90 days post-randomization.
15. Patients who cannot be taken off anticoagulants for at least 7 days post-surgery.
16. Patients with bilateral subacute or chronic SDH where both sides require surgery.

The Intention-To-Treat (ITT) population included all patients enrolled in the study who signed the patient ICF and were randomized. The modified Intention-To-Treat (mITT) population was a subset of the ITT population excluding the patients who did not successfully complete the treatment to which they were assigned.

Patient Demographics and Characteristics

There were no significant differences between the test and control groups for patient demographics and baseline characteristics (Table 1) and for baseline SDH characteristics (Table 2).

Table 1. Patient Demographics and Baseline Characteristics – ITT Population

Patient Demographics	Onyx™ LES MMA Embolization + Surgery	Surgery Only
	Test (N=197)	Control (N=203)
Age		
Mean ± SD (N)	73.0 ± 11.0 (197)	71.0 ± 11.3 (203)
Median (Range)	74.7 (21.7, 90.8)	72.5 (28.2, 90.2)
Sex		
Male	72.6% (143/197)	73.4% (149/203)
Female	27.4% (54/197)	26.6% (54/203)
Most Common Symptoms at Presentation		
Headaches	68.5% (135/197)	71.9% (146/203)
Gait Instability	71.1% (140/197)	67.5% (137/203)
Limb Weakness	58.4% (115/197)	57.6% (117/203)
Cognitive Impairment	45.2% (89/197)	45.3% (92/203)
Focal Neurological Deficit	34.5% (68/197)	42.4% (86/203)
Markwalder Grading Scale (MGS) Score at Presentation		
Mean ± SD (N)	1.4 ± 0.48 (197)	1.4 ± 0.49 (203)
Median (Range)	1 (1, 2)	1 (1, 2)
Modified Rankin Scale Score at Presentation		
Mean ± SD (N)	2.2 ± 1.12 (197)	2.3 ± 1.12 (203)
Median (Range)	2 (1, 5)	2 (1, 5)
Antiplatelet and/or Anticoagulant Usage at Onset of SDH Symptoms	38.1% (75/197)	38.9% (79/203)

Table 2. Site-Reported Baseline SDH Characteristics – ITT Population

Patient Demographics	Onyx™ LES MMA Embolization + Surgery	Surgery Only
	Test (N=197)	Control (N=203)
SDH Type		
Chronic	57.9% (114/197)	57.1% (116/203)
Subacute	42.1% (83/197)	42.9% (87/203)
Target Hemisphere		
Left	49.2% (97/197)	54.7% (111/203)
Right	50.8% (100/197)	45.3% (92/203)
Bilateral SDH	21.3% (42/197)	18.2% (37/203)
SDH characteristics		
Calcified	2.5% (5/197)	0.0% (0/203)
Homogeneous	27.9% (55/197)	30.5% (62/203)
Layering	51.3% (101/197)	46.8% (95/203)
Septated	45.2% (89/197)	38.4% (78/203)
Other	2.0% (4/197)	3.0% (6/203)
Hematoma Thickness (mm)		
Mean ± SD (N)	21.55 ± 6.276 (197)	21.42 ± 6.235 (203)
Median (Range)	21.0 (7.0, 39.0)	22.0 (7.0, 36.0)
Midline Shift (mm)		
Mean ± SD (N)	7.87 ± 3.608 (197)	8.55 ± 4.053 (203)
Median (Range)	8.0 (0.0, 19.0)	8.0 (0.0, 26.0)

Procedural Characteristics and Technical Success

The type of surgery administered was similar in the test and control groups. Burr hole surgery was performed in 53.6% (105/196) of patients in the test group and 51.0% (103/202) of patients in the control group. Craniotomy was performed in 46.4% (91/196) of patients in the test group and 49.0% (99/202) of patients in the control group.

NOTE: 1 patient in the test group withdrew consent prior to any treatment, and 1 patient in the control group was high-risk, hence surgery was not performed.

In the test group, radial access was performed in 39.8% (78/196) of patients. The Onyx™ LES vial was opened and embolization attempted in 185/197 patients (of the remaining 12 patients, 1 withdrew consent prior to any treatment and 11 were not eligible for embolization with Onyx™ LES due to presence of dangerous anatomical variants). Surgery was performed prior to the MMA embolization procedure in 42.2% (78/185) of patients. Embolization characteristics are provided in Table 3.

Table 3. Embolization Characteristics

Patient Characteristics	Onyx™ LES MMA Embolization + Surgery
	Test (N=185)*
Hemisphere Embolized	
Left	49.7% (92/185)
Right	46.5% (86/185)
Bilateral	3.8% (7/185)
Onyx™ Formulation	
Onyx™ 18 LES	95.1% (176/185)
Onyx™ 34 LES	3.8% (7/185)
Onyx™ 18 and Onyx™ 34 LES	1.1% (2/185)

*All patients for whom at least 1 vial of Onyx™ LES was opened and embolization attempted. 12 patients did not have an attempted embolization with Onyx™ LES.

Per the site, Onyx™ was successfully injected into the MMA in 100% (185/185) of patients. Similarly, per Imaging Core Lab assessment, 100% (185/185) of patients had successful embolization of the target vessel, with 1.6% (3/185) of patients exhibiting presence of reflux to non-target vessels (petrosal, collaterals). None of these patients exhibited any visual complications, stroke, facial palsy, or reflux-related complications.

Effectiveness Endpoints

The original primary effectiveness endpoint of the EMBOLISE study was CEC-adjudicated hematoma recurrence/progression requiring surgical drainage within 90 days post-treatment. However, based on discussions with the FDA, a primary composite endpoint was developed to incorporate clinical outcomes. This endpoint was developed after the completion of enrollment in the Surgery Cohort and collection of follow-up data. However, data analysis was pending when this primary endpoint was changed. The updated primary endpoint is a composite of the rate of hematoma recurrence/progression requiring surgical drainage within 90 days post-treatment, OR poor clinical outcome OR clinical deterioration at 90 days post-treatment. Poor clinical outcome is defined as MGS score 2-4, MSS score 0-3, or Glasgow Coma Scale (GCS) score 3-12 at 90 days. Clinical deterioration is defined as ≥ 1 point worsening in MGS , GCS, or MSS at 90 days compared to baseline (except MSS 5 at baseline → MSS 4 at 90 days).

The endpoint was designed to test superiority between test and control groups.

The primary endpoint was successfully met in the ITT and mITT populations (Table 4). Adjunctive MMA embolization with Onyx™ LES led to a statistically significant reduction in the primary composite endpoint (8.6% vs. 15.8% in the test group vs. the control group of the ITT population, respectively, relative risk 0.55, 95% confidence interval (CI) [0.30, 0.98], p=0.0330), demonstrating effectiveness for the treatment of symptomatic subacute or chronic SDH.

The outcome of CEC-adjudicated hematoma recurrence/progression requiring surgical drainage within 90 days post-treatment) with multiple imputation of missing outcomes, was successfully met in the ITT population and the mITT population (Table 5). Adjunctive MMA embolization with Onyx™ LES led to a statistically significant reduction in recurrence requiring surgical retreatment (4.1% vs. 11.3% in the test group vs. the control group, respectively, relative risk 0.36, 95% CI [0.11, 0.80]), demonstrating effectiveness for the treatment of symptomatic subacute or chronic SDH.

Table 5. Hematoma Recurrence/Progression Requiring Surgical Drainage Within 90 Days

CEC-Adjudicated Hematoma recurrence/ progression requiring surgical drainage within 90 days post-treatment	ITT		mITT	
	Onyx™ LES MMA Embolization + Surgery	Surgery Only	Onyx™ LES MMA Embolization + Surgery	Surgery Only
	Test (N=197)	Control (N=203)	Test (N=185)	Control (N=202)
Incidence[1,2] [95% CI]	4.1% [1.8%, 7.8%]	11.3% [7.3%, 16.5%]	3.2% [1.2%, 6.9%]	11.4% [7.4%, 16.6%]
Relative Risk [95% CI]	0.36 [0.11, 0.80]		0.28 [0.08, 0.68]	

[1]Outcome is imputed for patients who failed to attend the 90-day evaluation visit (based on completion of the 90-day visit or the 90-day imaging requirement) and who did not have CEC-adjudicated hematoma recurrence/progression requiring surgical drainage within 90 days post-treatment.

[2]Does not include an additional 3 patients in the control group who were retreated outside the protocol (with MMA embolization only), despite experiencing hematoma recurrence/progression. As surgical retreatment was not done, they did not contribute to the primary endpoint.

Table 4. Results of the Primary Endpoint

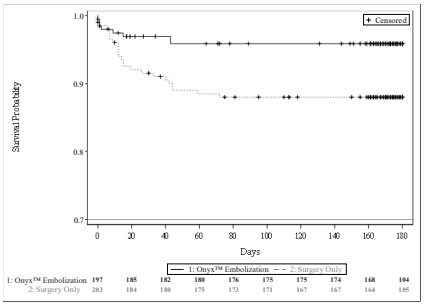
CEC-Adjudicated Hematoma recurrence/ progression requiring surgical drainage within 90 days post-treatment, OR poor clinical outcome OR clinical deterioration at 90 days post-treatment[1]	ITT		mITT	
	Onyx™ LES MMA Embolization + Surgery	Surgery Only	Onyx™ LES MMA Embolization + Surgery	Surgery Only
	Test (N=197)	Control (N=203)	Test (N=185)	Control (N=202)
Incidence[2] [95% CI]	8.6% [5.1%, 13.5%]	15.8% [11.0%, 21.5%]	7.6% [4.2%, 12.4%]	15.8% [11.1%, 21.6%]
Relative Risk [95% CI]	0.55 [0.30, 0.98]		0.48 [0.25, 0.90]	
Fisher's exact test p-value	0.0330		0.0123	

[1]Poor clinical outcome is defined as MGS score 2-4, MSS score 0-3, or GCS score 3-12. Clinical deterioration is defined as ≥ 1 point worsening in MGS, GCS, or MSS at 90 days compared to baseline (except MSS 5 at baseline → MSS 4 at 90 days).

[2]Outcome is imputed for patients who failed to attend the 90-day evaluation visit due to early study withdrawal or loss to follow-up, including patients who exited due to death prior to the 90-day evaluation and had no CEC-adjudicated hematoma recurrence/progression requiring surgical drainage during follow-up. Outcome is also imputed for patients missing one or more of the MGS, MSS, and GCS evaluations at baseline or 90 days, unless the patient had evidence of CEC-adjudicated hematoma recurrence/progression requiring surgery within 90 days post-treatment.

All retreatments in the test and control groups occurred within 90 days; the majority occurred within 30 days (75.0% [6/8] vs. 70.8% [17/24] of test and control patients, respectively). Figure 2 shows a Kaplan-Meier curve of freedom from re-intervention through study follow-up (including the 3 control group patients retreated with MMA embolization alone who did not contribute to the primary endpoint).

Figure 2. Kaplan-Meier Curve of Freedom from Re-Intervention Through Study Follow-Up



The clinical secondary endpoint (non-inferiority assessment of deterioration in neurologic function at 90 days [defined as having mRS < 3 at baseline and ≥ 3 at 90 days or having mRS ≥ 3 at baseline and having an increase of ≥ 1 mRS unit at 90 days]) was also met in the mITT population (Table 6). Deterioration in neurologic function was non-inferior in the test group vs. the control group (12.7% vs. 9.8% of patients in the test group vs. the control group, respectively, risk difference 2.87%, 95% CI [-4.20%, 9.93%], non-inferiority p=0.0057).

Table 6. Clinical Secondary Endpoint Results – mITT Population

	Onyx™ LES MMA Embolization + Surgery	Surgery Only
	Test (N=185)	Control (N=202)
Incidence of Deterioration in Neurologic Function[1] [95% CI]	12.7% (21/166) [8.0%, 18.7%]	9.8% (18/184) [5.9%, 15.0%]
Risk Difference [95% CI]	2.87% [-4.20%, 9.93%]	
Non-inferiority P-value[2]	0.0057	

[1] Deterioration is defined as having mRS < 3 at baseline and ≥ 3 at 90 days, or having mRS ≥ 3 at baseline and having an increase of ≥ 1 point at 90 days. mRS score of 6 (death) is imputed for patients who died before the 90 day assessment.

[2] P-value for the non-inferiority test. If the upper 95% confidence limit of the difference is < 0.12, the null hypothesis is rejected, and the Farrington-Manning test indicates strong evidence of non-inferiority.

Safety Outcomes and Adverse Events

Safety Endpoints

The clinical events committee (CEC) assessed the safety endpoints of CEC-adjudicated device-related and procedure-related adverse events (Table 7).

Table 7. CEC Adjudicated Safety Endpoints: Device- and Procedure-Related Adverse Events - mITT Population

Outcome	Onyx™ LES MMA Embolization + Surgery
	Test (N=185)
Serious adverse events (SAEs) related to embolization and surgery procedure, through 30 days	10.8% (20/185) [24]
SAEs related to embolization procedure only, through 30 days	2.2% (4/185) [4]
Onyx™ LES device-related SAEs through 30 days	0.0% (0/185) [0]
Onyx™ LES device-related AEs through 90 days	0.0% (0/185) [0]
Onyx™ LES device-related AEs through 180 days	0.0% (0/185) [0]
Numbers are: % (n/N) [# of events]	

The CEC assessed the safety endpoints of neurological death through 90 days (Table 8) and through 180 days (Table 9). In the test group, in most cases, the index SDH was stable/improved prior to death. Additionally, almost all deaths were due to baseline SDH disease; none were due to Onyx™ LES or to the embolization procedure.

Table 8. CEC Adjudicated Safety Endpoints: Neurological Death Through 90 Days - mITT Population

Neurological Deaths Through 90 Days	Onyx™ LES MMA Embolization + Surgery	Surgery Only
	Test (N=185)	Control (N=202)
Overall	4.9% (9/185)	2.0% (4/202)
Classification based on SDH progression		
Subdural disease was stable/improved at last follow-up[1]	3.2% (6/185)	1.0% (2/202)
Subdural disease worsened >10% at last follow-up[1]	0.5% (1/185)	0.5% (1/202)
Indeterminate[2]	1.1% (2/185)	0.5% (1/202)
Classification based on causality		
Related to SDH disease only (i.e., unrelated to treatment/procedure)	4.3% (8/185)	1.0% (2/202)
Related to Onyx™ LES device	0.0% (0/185)	N/A
Related to embolization procedure	0.0% (0/185)	N/A
Related to surgery procedure	0.5% (1/185)	1.0% (2/202)

[1]Defined as when the change in mean SDH thickness at the last follow-up visit image compared to baseline (24-hour post-treatment) was ≤ 10% (stable/improved) or > 10% (worsened), per Core Lab assessment.
[2]No available follow-up image after baseline.
Numbers are: % (n/ N)

Table 9. CEC Adjudicated Safety Endpoints: Neurological Death Through 180 Days - mITT Population

Neurological Deaths Through 180 Days	Onyx™ LES MMA Embolization + Surgery	Surgery Only
	Test (N=185)	Control (N=202)
Overall	5.9% (11/185)	3.0% (6/202)
Classification based on SDH progression		
Subdural disease was stable/improved at last follow-up[1]	4.3% (8/185)	1.5% (3/202)
Subdural disease worsened >10% at last follow-up[1]	0.5% (1/185)	1.0% (2/202)
Indeterminate[2]	1.1% (2/185)	0.5% (1/202)
Classification based on causality		
Related to SDH disease only (i.e., unrelated to treatment/procedure)	5.4% (10/185)	1.5% (3/202)
Related to Onyx™ LES	0.0% (0/185)	N/A
Related to embolization procedure	0.0% (0/185)	N/A
Related to surgery procedure	0.5% (1/185)	1.5% (3/202)

[1]Defined as when the change in mean SDH thickness at the last follow-up visit image compared to baseline (24-hour post-treatment) was ≤ 10% (stable/improved) or > 10% (worsened), per Core Lab assessment.
[2]No available follow-up image after baseline.
Numbers are: % (n/ N)

Deaths

Per CEC adjudication, mITT population: A total of 14/185 (7.6%) patients in the test group and 8/202 (4.0%) patients in the control group died through study follow-up. In the test group, 11 deaths were neurologic. A total of 10/185 deaths were related to the SDH disease and 1/185 was related to the surgery procedure; none (0%) were related to the Onyx™ LES device or the MMA embolization procedure. In the control group, 6 deaths were neurologic. A total of 3/202 deaths were related to the SDH disease and 3/202 deaths were related to the surgery procedure.

Adverse Events

Per CEC adjudication, through 180 days: No adverse events were related to the Onyx™ LES device. Four SAEs were related to the MMA embolization procedure alone, consisting of 1 event each of arterial rupture, ischemic stroke, cerebellar infarction, and a device malfunction (guide catheter device breakage). In the test group, no (0%) patients exhibited ipsilateral visual symptoms, Onyx™ LES migration, or catheter entrapment. A total of 3/185 (1.6%) patients exhibited non-serious access site complications consisting of 1 event each of skin laceration, vascular access site bruising, and vasospasm. A summary of all CEC-adjudicated AEs is provided in Table 10.

Table 10. CEC-Adjudicated Events Through 180 Days[1] - mITT Population (N=387)							
Adverse Event Term		Onyx™ LES MMA Embolization + Surgery			Surgery Only		
		Test (N=185)			Control (N=202)		
System Organ Class	Preferred Term	All AEs	SAEs	Non-SAEs	All AEs	SAEs	Non-SAEs
Total	**Total**	**50.8% (94/185) [201]**	**34.1% (63/185) [120]**	**31.4% (58/185) [81]**	**42.6% (86/202) [181]**	**34.2% (69/202) [116]**	**18.8% (38/202) [65]**
Blood and lymphatic system disorders	Total	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.0% (0/202) [0]	0.5% (1/202) [1]
	Anaemia	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Thrombocytopenia	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.0% (0/202) [0]	0.5% (1/202) [1]
Cardiac disorders	Total	4.3% (8/185) [9]	3.8% (7/185) [8]	0.5% (1/185) [1]	1.0% (2/202) [2]	1.0% (2/202) [2]	0.0% (0/202) [0]
	Acute myocardial infarction	1.1% (2/185) [2]	1.1% (2/185) [2]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Atrial fibrillation	1.6% (3/185) [3]	1.1% (2/185) [2]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Cardiac arrest	1.1% (2/185) [2]	1.1% (2/185) [2]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Cardiac failure congestive	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Cardio-respiratory arrest	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
Ear and labyrinth disorders	Total	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.0% (0/202) [0]	0.5% (1/202) [1]
	Vertigo	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.0% (0/202) [0]	0.5% (1/202) [1]
Eye disorders	Total	1.1% (2/185) [2]	0.0% (0/185) [0]	1.1% (2/185) [2]	1.0% (2/202) [2]	0.5% (1/202) [1]	0.5% (1/202) [1]
	Diplopia	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.0% (0/202) [0]	0.5% (1/202) [1]
	Eye pain	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Visual impairment	1.1% (2/185) [2]	0.0% (0/185) [0]	1.1% (2/185) [2]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
Gastrointestinal disorders	Total	4.9% (9/185) [9]	3.8% (7/185) [7]	1.1% (2/185) [2]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Dysphagia	4.9% (9/185) [9]	3.8% (7/185) [7]	1.1% (2/185) [2]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
General disorders and administration site conditions	Total	1.6% (3/185) [3]	0.5% (1/185) [1]	1.1% (2/185) [2]	2.0% (4/202) [4]	1.0% (2/202) [2]	1.0% (2/202) [2]
	Asthenia	1.1% (2/185) [2]	0.0% (0/185) [0]	1.1% (2/185) [2]	1.0% (2/202) [2]	0.5% (1/202) [1]	0.5% (1/202) [1]
	Gait disturbance	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	1.0% (2/202) [2]	0.5% (1/202) [1]	0.5% (1/202) [1]
Hepatobiliary disorders	Total	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	1.0% (2/202) [2]	1.0% (2/202) [2]	0.0% (0/202) [0]
	Cirrhosis alcoholic	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Hepatic cirrhosis	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
Infections and infestations	Total	8.1% (15/185) [18]	5.9% (11/185) [13]	2.7% (5/185) [5]	5.4% (11/202) [14]	5.0% (10/202) [12]	1.0% (2/202) [2]
	Abscess	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Brain abscess	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	COVID-19	1.6% (3/185) [3]	0.5% (1/185) [1]	1.1% (2/185) [2]	0.5% (1/202) [1]	0.0% (0/202) [0]	0.5% (1/202) [1]
	Clostridium difficile infection	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Necrotising fasciitis	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Pneumonia	1.6% (3/185) [3]	1.1% (2/185) [2]	0.5% (1/185) [1]	1.5% (3/202) [3]	1.5% (3/202) [3]	0.0% (0/202) [0]
	Pneumonia aspiration	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Postoperative wound infection	1.1% (2/185) [2]	1.1% (2/185) [2]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]

Table 10. CEC-Adjudicated Events Through 180 Days[1] - mITT Population (N=387)							
Adverse Event Term		Onyx™ LES MMA Embolization + Surgery			Surgery Only		
		Test (N=185)			Control (N=202)		
System Organ Class	Preferred Term	All AEs	SAEs	Non-SAEs	All AEs	SAEs	Non-SAEs
Infections and infestations	Sepsis	2.2% (4/185) [4]	2.2% (4/185) [4]	0.0% (0/185) [0]	1.0% (2/202) [2]	1.0% (2/202) [2]	0.0% (0/202) [0]
	Subdural abscess	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	1.0% (2/202) [2]	1.0% (2/202) [2]	0.0% (0/202) [0]
	Urinary tract infection	1.1% (2/185) [2]	0.0% (0/185) [0]	1.1% (2/185) [2]	1.5% (3/202) [3]	1.0% (2/202) [2]	0.5% (1/202) [1]
	Wound infection	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
Injury, poisoning and procedural complications	Total	14.6% (27/185) [31]	7.6% (14/185) [17]	7.6% (14/185) [14]	20.8% (42/202) [49]	16.8% (34/202) [39]	5.0% (10/202) [10]
	Alcohol poisoning	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [2]	0.5% (1/202) [2]	0.0% (0/202) [0]
	Craniocerebral injury	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Extradural haematoma	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Fall	1.6% (3/185) [3]	1.1% (2/185) [2]	0.5% (1/185) [1]	1.5% (3/202) [3]	1.0% (2/202) [2]	0.5% (1/202) [1]
	Multiple injuries	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Pneumocephalus	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Procedural complication	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Skin laceration	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Subdural haematoma	11.4% (21/185) [24]	7.0% (13/185) [15]	4.9% (9/185) [9]	17.8% (36/202) [40]	14.4% (29/202) [31]	4.5% (9/202) [9]
	Vascular access site bruising	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
Investigations	Total	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Magnetic resonance imaging head abnormal	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
Metabolism and nutrition disorders	Total	1.6% (3/185) [3]	1.6% (3/185) [3]	0.0% (0/185) [0]	1.5% (3/202) [4]	1.5% (3/202) [4]	0.0% (0/202) [0]
	Failure to thrive	1.6% (3/185) [3]	1.6% (3/185) [3]	0.0% (0/185) [0]	1.0% (2/202) [2]	1.0% (2/202) [2]	0.0% (0/202) [0]
	Hyponatraemia	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Malnutrition	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
Musculoskeletal and connective tissue disorders	Total	1.6% (3/185) [3]	1.1% (2/185) [2]	0.5% (1/185) [1]	1.5% (3/202) [4]	1.5% (3/202) [3]	0.5% (1/202) [1]
	Arthralgia	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Compartment syndrome	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Muscular weakness	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	1.0% (2/202) [2]	0.5% (1/202) [1]	0.5% (1/202) [1]
	Myalgia	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
Nervous system disorders	Total	35.1% (65/185) [97]	22.7% (42/185) [55]	18.4% (34/185) [42]	28.2% (57/202) [91]	18.8% (38/202) [46]	15.3% (31/202) [45]
	Amnesia	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Aphasia	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.0% (0/202) [0]	0.5% (1/202) [1]
	Ataxia	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Cerebellar haemorrhage	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Cerebellar infarction	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Cerebral haemorrhage	1.1% (2/185) [2]	1.1% (2/185) [2]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]

Table 10. CEC-Adjudicated Events Through 180 Days[1] - mITT Population (N=387)							
Adverse Event Term		Onyx™ LES MMA Embolization + Surgery			Surgery Only		
		Test (N=185)			Control (N=202)		
System Organ Class	Preferred Term	All AEs	SAEs	Non-SAEs	All AEs	SAEs	Non-SAEs
Nervous system disorders	Cerebral infarction	2.2% (4/185) [4]	1.1% (2/185) [2]	1.1% (2/185) [2]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Cerebral vasoconstriction	1.1% (2/185) [2]	0.0% (0/185) [0]	1.1% (2/185) [2]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Cognitive disorder	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	1.0% (2/202) [2]	0.0% (0/202) [0]	1.0% (2/202) [2]
	Dementia	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Dizziness	1.6% (3/185) [3]	0.0% (0/185) [0]	1.6% (3/185) [3]	0.5% (1/202) [1]	0.0% (0/202) [0]	0.5% (1/202) [1]
	Dural arteriovenous fistula	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Dysarthria	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Encephalopathy	11.4% (21/185) [22]	7.6% (14/185) [15]	3.8% (7/185) [7]	9.9% (20/202) [23]	7.9% (16/202) [17]	2.5% (5/202) [6]
	Haemorrhage intracranial	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Head discomfort	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.0% (0/202) [0]	0.5% (1/202) [1]
	Headache	9.2% (17/185) [17]	0.5% (1/185) [1]	8.6% (16/185) [16]	9.4% (19/202) [19]	1.0% (2/202) [2]	8.4% (17/202) [17]
	Hepatic encephalopathy	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Hypoaesthesia	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.0% (0/202) [0]	0.5% (1/202) [1]
	Intracranial artery dissection	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Ischaemic stroke	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	1.0% (2/202) [2]	1.0% (2/202) [2]	0.0% (0/202) [0]
	Motor dysfunction	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.0% (0/202) [0]	0.5% (1/202) [1]
	Nervous system disorder	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.0% (0/202) [0]	0.5% (1/202) [1]
	Neurological decompensation	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	2.0% (4/202) [4]	0.5% (1/202) [1]	1.5% (3/202) [3]
	Neurological symptom	5.4% (10/185) [10]	4.3% (8/185) [8]	1.1% (2/185) [2]	3.0% (6/202) [6]	2.0% (4/202) [4]	1.0% (2/202) [2]
	Neuropathy peripheral	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Paraesthesia	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	1.5% (3/202) [4]	0.0% (0/202) [0]	1.5% (3/202) [4]
	Seizure	9.2% (17/185) [18]	7.6% (14/185) [15]	1.6% (3/185) [3]	8.4% (17/202) [17]	6.9% (14/202) [14]	1.5% (3/202) [3]
	Somnolence	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Speech disorder	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Status epilepticus	1.1% (2/185) [2]	1.1% (2/185) [2]	0.0% (0/185) [0]	1.0% (2/202) [2]	1.0% (2/202) [2]	0.0% (0/202) [0]
	Subarachnoid haemorrhage	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Subdural hygroma	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	1.0% (2/202) [2]	0.5% (1/202) [1]	0.5% (1/202) [1]
	Syncope	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.0% (0/202) [0]	0.5% (1/202) [1]
Product issues	Total	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Device breakage	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
Psychiatric disorders	Total	1.1% (2/185) [2]	0.0% (0/185) [0]	1.1% (2/185) [2]	1.0% (2/202) [2]	0.0% (0/202) [0]	1.0% (2/202) [2]
	Confusional state	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Delirium	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Hallucination	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.0% (0/202) [0]	0.5% (1/202) [1]
	Insomnia	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.0% (0/202) [0]	0.5% (1/202) [1]

Table 10. CEC-Adjudicated Events Through 180 Days[1] - mITT Population (N=387)							
Adverse Event Term		Onyx™ LES MMA Embolization + Surgery			Surgery Only		
		Test (N=185)			Control (N=202)		
System Organ Class	Preferred Term	All AEs	SAEs	Non-SAEs	All AEs	SAEs	Non-SAEs
Respiratory, thoracic and mediastinal disorders	Total	3.8% (7/185) [7]	2.2% (4/185) [4]	1.6% (3/185) [3]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Pleural effusion	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Pulmonary embolism	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Pulmonary fibrosis	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Pulmonary oedema	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Respiratory failure	1.6% (3/185) [3]	1.6% (3/185) [3]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Rhinalgia	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
Skin and subcutaneous tissue disorders	Total	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Decubitus ulcer	0.0% (0/185) [0]	0.0% (0/185) [0]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
Surgical and medical procedures	Total	1.6% (3/185) [3]	1.1% (2/185) [2]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Craniotomy	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Gastrostomy	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Intra-cerebral aneurysm operation	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
Vascular disorders	Total	5.4% (10/185) [11]	3.2% (6/185) [6]	2.7% (5/185) [5]	1.0% (2/202) [2]	1.0% (2/202) [2]	0.0% (0/202) [0]
	Arterial rupture	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Deep vein thrombosis	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Hypertensive urgency	0.5% (1/185) [1]	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/202) [1]	0.5% (1/202) [1]	0.0% (0/202) [0]
	Hypotension	1.6% (3/185) [3]	1.6% (3/185) [3]	0.0% (0/185) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Vasospasm	2.2% (4/185) [4]	0.0% (0/185) [0]	2.2% (4/185) [4]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]
	Vessel perforation	0.5% (1/185) [1]	0.0% (0/185) [0]	0.5% (1/185) [1]	0.0% (0/202) [0]	0.0% (0/202) [0]	0.0% (0/202) [0]

Numbers are: % (n/N) [# of events]
[1]% (n/N) numbers are percent of subjects who experienced one or more episodes of the event.
'Events' numbers are total count of episodes of each type of event among all subjects in the cohort.

Clinical Trial Conclusions

In conclusion, the EMBOLISE study met its primary endpoint and demonstrated superiority of adjunctive MMA embolization with Onyx™ LES (Onyx™ LES + surgery, treatment) over surgery alone (control) in preventing hematoma recurrence/ progression requiring surgical drainage. The secondary clinical endpoint demonstrated non-inferiority of adjunctive MMA embolization with Onyx™ LES in the rate of deterioration in neurologic function. The safety profile was similar between the test and control groups , although there was a numerical difference in the number of deaths between the test and control groups. Overall, adjunctive MMA embolization with Onyx™ LES was associated with significantly reduced rates of reoperation without compromising neurologic function or safety.

CLINICAL STUDY RESULTS - BRAIN AVM

Study Purpose

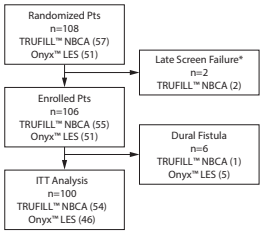
The purpose of this study was to assess the safety and effectiveness of Onyx™ LES in the presurgical embolization of bAVMs. Device safety was assessed by comparing the incidence of adverse events. The primary efficacy endpoint was the angiographic reduction in bAVM size (volume) achieved. A level of 50% or greater reduction in size was established as a criterion for success. The objective was to demonstrate that the Onyx™ LES is no worse than TRUFILL™ NBCA, a legally marketed bAVM embolization device, in terms of effectiveness within a specified clinical tolerance (20%).

Design

This study was designed as a prospective, randomized, multi-center clinical comparison of the Onyx™ LES to the Cerenovus TRUFILL™ n-Butyl cyanoacrylate (TRUFILL™ NBCA) liquid embolic agent for the presurgical treatment of bAVMs. The primary endpoint of the study required 100 patients to be evaluated for effectiveness. One hundred and eight patients were randomized: two of these patients were late screen failures, having been deemed anatomically unsuitable for embolization by the treating physician. Thus, 106 patients were enrolled and randomized, on a 1:1 basis, at 20 clinical sites in the U.S. to either embolization with the Onyx™ LES or TRUFILL™ NBCA resulting in 51 patients in the Onyx™ LES group and 55 patients in the TRUFILL™ NBCA group. Six patients were deemed by the core lab to be dural fistulae subjects, and thus were

excluded from the efficacy analysis, resulting in 100 patients evaluated for efficacy. Demographic information, including bAVM characteristics, is presented on 102 patients, which includes information on the 2 patients who were late screen failures. A summary of patient enrollment is provided in Figure 3.

Figure 3. Efficacy Endpoint Patient Flow



*Late screen failures: anatomically unsuitable for embolization.

An additional 17 patients were enrolled under a continued access provision. Safety was evaluated for all 117 patients in the Intention to Treat (ITT) cohort, which includes all patients in which treatment of the assigned device was attempted. Safety was assessed based on the nature and severity of adverse events, and is reported in Table 17.

- All patients with a bAVM in the cerebral cortex, cerebellum or dura mater of a Spetzler-Martin grade I-IV were randomized to either the Onyx™ LES or TRUFILL™ NBCA treatment arms. For patients randomized to Onyx™ LES, the formulation used (Onyx™ LES 18 alone, Onyx™ LES 34 alone, or combination of Onyx™ LES 18 and 34) was at the physician's discretion. For patients randomized to TRUFILL™ NBCA, the oil:TRUFILL™ NBCA ratio used was also at the physician's discretion. Patients underwent embolization procedure(s) to reduce the size of the bAVM prior to surgical resection. Neurological assessments (i.e., NIH scale, Barthel Index, and Glasgow Index) were performed prior to and post embolization and/or surgical resection, when surgery was performed. Although patients were to undergo total surgical resection as an enrollment criterion, 6 patients in the TRUFILL™ NBCA group and 5 patients in the Onyx™ LES group did not undergo total resection.

Methods

Patients were evaluated for potential enrollment based on the inclusion and exclusion criteria of the protocol, as described below:

Inclusion Criteria:

- The patient has a bAVM in the cerebral cortex, cerebellum or dura mater.
- The bAVM has a Spetzler-Martin grade of I – IV.
- The patient is a candidate for surgical resection of the bAVM post embolization.
- The patient is clinically and neurologically stable for a minimum of 24 hours prior to the embolization procedure.
- The patient can be of any age.

Exclusion Criteria

- The patient has a bAVM with a high flow AV fistula that the investigator has determined to be unsuitable for embolization.
- The bAVM has a Spetzler-Martin grade of V.
- The patient is participating in another research study involving another investigational device, procedure or drug.
- The bAVM has been previously embolized with another agent.

Review of patient demographics and baseline bAVM characteristics show no differences between the Onyx™ LES and TRUFILL™ NBCA groups. bAVM size was found to be slightly higher in the Onyx™ LES group, however this difference was not statistically significant. Both groups had the majority of patients treated with bAVMs having a Spetzler-Martin grade of either II or III. All other bAVM characteristics were comparable between the two groups.

Patient Demographics and Characteristics

Patient demographics and bAVM characteristics are presented in Table 11 and Table 12.

Table 11. Patient Demographics

Patient Demographics	Group	
	TRUFILL™ NBCA (n=56)	Onyx™ LES (n=46)
Age (yrs):		
Mean+/-SD (N)	35.1 ± 14.3 (56)	40.3 ± 16.3 (46)
Median (Range):	36.0 (10.0 – 66.0)	42.5 (7.0 – 72.0)
Gender:		
Male	48.2% (27/56)	43.5% (20/46)
Female	51.7% (29/56)	56.5% (26/46)
Demographics include 2 late screen failure patients		

Table 12. bAVM Characteristics*

(n=103 bAVMs in n=102 pts) Pretreatment Assessment		TRUFILL™ NBCA (n=57 bAVMs in 56 patients)	Onyx™ LES (n=46 bAVMs in 46 patients)
bAVM Location	Right	55.4% (31/56)	63.0 % (29/46)
	Left	41.1% (23/56)	34.8 % (16/46)
	Midline	3.6 % (2/56)	2.2 % (1/46)
bAVM Located in eloquent area of Brain		48.2% (27/56)	45.7 % (21/46)
Venous Drainage	Deep	8.9 % (5/56)	15.2 % (7/46)
	Superficial	62.5% (35/56)	63.0 % (29/46)
	Both	28.6% (16/56)	21.7 % (10/46)
Spetzler-Martin Grade			
	I	25.0% (14/56)	10.9 % (5/46)
	II	25.0 % (14/56)	43.5% (20/46)
	III	30.4% (17/56)	26.1 % (12/46)
	IV	19.6% (11/56)	19.6 % (9/46)
bAVM Size (Core Lab, mm3)			
	Mean+/- SD	16.0+/- 20.0	26.3+/- 45.2
	Median	8.1	13.6
	Range	0.08-94.9	0.17-290.5
*bAVM Characteristics include 2 late screen failure patients			

Procedural Characteristics

Upon enrollment, a baseline clinical neurological examination was performed and grading scales including Barthel Index, Glasgow Coma Scale (GCS) and NIH Stroke Scale (NIHSS) were recorded. In addition, baseline CT, MRI, and/or angiograms were performed for complete characterization of the bAVM prior to randomization. Following randomization, patients were embolized as deemed appropriate by the investigator. The physician determined the number of embolization stages and the percent bAVM reduction based on factors specific to each patient, such as bAVM size, number of feeders, fistulous connections, and location relative to eloquent territory. The majority of patients in each group underwent one embolization procedure. The number of embolization procedures ranged from one to seven, as summarized in the Table 13. In the Onyx™ LES group 33 patients were treated with the Onyx™ LES 18 formula, 2 patients were treated with the Onyx™ LES 34 formula and 11 patients were treated with both formulations.

Coils were used as adjunctive therapy in 23 of 91 TRUFILL™ NBCA procedures and 8 of 82 Onyx™ LES procedures. One Onyx™ LES patient received a single embolization treatment with the Onyx™ LES; the second embolization attempt was a failure for the Onyx™ LES delivery, and the patient was crossed over to treatment with TRUFILL™ NBCA. Two patients in the TRUFILL™ NBCA group received PVA (Table 13).

Table 13. Embolization Procedures Per Patient

# of Embolization Procedures	TRUFILL™ NBCA (n=54)		Onyx™ LES (n=46)	
	# of Pts	% of Pts	# of Pts	% of Pts
1	34	63.0%	26	56.5%
2	9	16.7%	11	23.9%
3	7	13.0%	6	13.0%
4	2	3.7%	1	2.2%
5	2	3.7%	1	2.2%
6	0	0.0%	0	0.0%
7	0	0.0%	1	2.2%
Total # Pts	54	100%	46	100%
Total Procedures	91		82	
Avg # Procs per Pt (min - max)	1.7 (1 - 5)		1.8 (1 - 7)	
Number of days between patient's first and last embolization procedure	Range: 1 – 197 days		Range: 2 – 408 days	

After each embolization procedure, patients were neurologically evaluated using the same scales as pre-procedure upon completion of the embolization phase, patients were referred for surgery. If, in the physician's opinion, surgical treatment was not an option, other nonsurgical courses of treatment including radiosurgery or no further treatment were implemented. Patients that were completely resected received a final neurological examination with grading scale assessments as a final evaluation of the protocol. Those patients with bAVMs that were not completely resected underwent follow-up evaluations at 3 and 12 months. The follow-up assessments included a complete neurological examination with grading scales including Barthel Index, Glasgow Outcome Score (GOS) and NIH Stroke Scale (NIHSS) and evaluation of safety.

Eleven patients were not completely resected and will be followed for 3 years. Of these 11 patients, 5 patients were treated with the Onyx™ LES and 6 were treated with TRUFILL™ NBCA. Six patients, 1 Onyx™ LES and 5 TRUFILL™ NBCA underwent radiosurgery. Two Onyx™ LES patients had partial resections and radiosurgery. One TRUFILL™ NBCA patient had only partial resection. Two Onyx™ LES patients had no further treatment following embolizations.

Effectiveness Endpoints

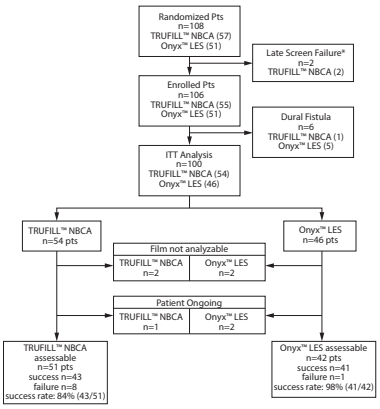
The primary effectiveness measure was technical success as measured by angiographic reduction in bAVM size (volume) of 50% or greater as assessed by core laboratory. Angiographic size reduction is defined as the change from the original bAVM size prior to any embolization procedure, to the bAVM size after the patient's final embolization procedure.

The results for the primary effectiveness endpoint demonstrate that the two products are comparable with regard to bAVM occlusion efficacy, and thus, the primary study hypothesis (i.e., Onyx™ LES is no worse than TRUFILL™ NBCA in terms of bAVM obliteration defined as ≥ 50% occlusion as assessed by core angiographic laboratory) was achieved using an Intention to Treat analysis (ITT) approach (Table 14).

An analysis for the primary effectiveness endpoint was performed with all those patients in the Intent-to-Treat (ITT) population in which the core lab was able to make an assessment of the degree of bAVM occlusion. Each patient was analyzed based on their treatment assignment regardless of course of treatment and evaluated after the final stage of embolization prior to surgical intervention.

A summary of the Intention-to-Treat analysis of patient flow with results is provided in Figure 4.

Figure 4. Analysis Flowchart



*Late screen failures: anatomically unsuitable for embolization.

**Patients ongoing: continuing embolization at time of data closure.

Primary endpoint analysis demonstrates non-inferiority of the Onyx™ LES device to TRUFILL™ NBCA. The Primary Endpoint Summary analysis is presented in Table 14.

Table 14. Primary Endpoint Summary

Core Lab Angiographic Success	TRUFILL™ NBCA (n= 54)	Onyx™ LES (n= 46)	Difference [95% CI]	Relative Risk [95% CI]
Intent-to-Treat Analysis	84.3% (43/51)	97.6% (41/42)	13.3% [2.3%, 24.3%]	1.16 [1.01,1.32]

Diff = Onyx – n-BCA; SE = sqrt(p1q1/n1+p2q2/n2); CI = Diff±1.96*SE

RR = Onyx/n-BCA; SE = sqrt{(1- p1)/ n11+(1- p2)/ n21}; CI = RR*exp(±1.96*SE)

The study had two secondary effectiveness endpoints: surgical blood loss and surgical resection time. There was considerable variability in these endpoints primarily due to the complexity of this disease state and the associated surgery for resection. No statistically significant differences were observed for either of these two secondary endpoints (Table 15).

Table 15. Secondary Effectiveness Endpoint Summary

Secondary Endpoints	TRUFILL™ NBCA* (n= 54)	Onyx™ LES* (n= 46)
Blood loss index		
Mean±sd (n)	892 ± 1067 (44)	1127 ± 1401 (43)
Median	475	550
Range (min, max)	100-5000	50-6550
Surgical resection time		
Mean±sd (n)	411 ± 201 (42)	399 ± 179 (42)
Median	344	366
Range (min, max)	150, 1019	82, 940

* A total of 89 patients had surgical resection of their bAVM (either total or partial), 46 patients in the n-BCA group and 43 patients in the Onyx™ LES group. Data on blood loss was available for 44 patients in the n-BCA group and 43 patients in the Onyx™ LES group. Data on surgical resection time was available for 42 patients in the n-BCA group and 42 patients in the Onyx™ LES group.

Safety Endpoints

Safety was assessed by the nature and severity of adverse events. The adverse events are shown in Table 17.

Deaths

There were 3 deaths reported in patients treated with the Onyx™ LES: two patients died during the clinical study period and 1 patient died after study follow-up was completed. In all cases, patients underwent surgical resection following embolization. The first patient developed intra- and peri-operative bleeding which resulted in a hematoma and infarction. The patient expired following withdrawal of care. The second patient had a large post-surgical middle cerebral artery (MCA) infarction and expired following withdrawal of care. The third patient who died following study follow-up completion sustained a significant neurological deficit after a surgery-related hemorrhage and required long term skilled nursing home care. The patient died several months after discharge in the nursing home. These deaths were not attributed to the device.

The possible role of the Onyx™ LES in the patient deaths, if any, is unknown.

The technical/procedural events encountered during embolization were similar for the two groups except for delivery catheter removal difficulty, which occurred six (6) times in five (5) patients in the Onyx™ LES group and in only one (1) patient in the TRUFILL™ NBCA group. All catheters in the Onyx™ LES group were able to be removed. The catheter in the TRUFILL™ NBCA group remained in the patient.

Table 16 summarizes the technical/procedural events related to the respective embolic agents:

Table 16. Technical/Procedural Events – Embolic Agent*

EVENT NAME	TRUFILL™ NBCA N=63		Onyx™ LES N=54	
Delivery Catheter removal difficulty	1	1 (1.6%)	6	5 (9.3%)
Poor penetration/ visualization	0	0 (0%)	6	5 (9.3%)
Poor visualization of Onyx	0	0 (0%)	1	1 (1.9%)
Embolization of unintended vessel	7	6 (9.5%)	0	0 (0%)
Premature polymerization time	3	3 (4.8%)	0	0 (0%)
Prolonged polymerization time	5	5 (7.9%)	0	0 (0%)

*Includes 17 continued access patients

Adverse Events

Potential Adverse Effects of the Device on Health

- A prospective, randomized, multi-center clinical trial compared Onyx™ LES to the TRUFILL™ n-Butyl cyanoacrylate (TRUFILL™ NBCA) liquid embolic system for the presurgical treatment of bAVMs. The primary endpoint of the study required 100 patients to be evaluated for effectiveness. An additional 17 patients were enrolled under a continued access provision. Safety was evaluated for all 117 patients in the Intention to Treat (ITT) cohort, which includes all patients in which treatment of the assigned device was attempted. Safety was assessed based on the nature and severity of adverse events.
- The safety profile for the two groups was comparable. Many of the events occurred during, or post surgery, as opposed to during, or post embolization, with the embolization agents.
- Two patients died during the course of the clinical trial. Both deaths occurred in the Onyx™ LES group and both occurred following surgical resection. A third death occurred after the patient had been discharged to a rehabilitation center for persistent neurological deficits, but the patient had completed study follow-up.

The Table 17 provides a summary of the adverse events that occurred during the study.

The following events occurred in one patient each in the Onyx™ LES group and did not occur in the TRUFILL™ NBCA group: catheter shaft rupture, delivery catheter rupture, fragmentation of the Onyx™ LES, hypoxia, laryngospasm, peptic ulcer disease, psychotic episode, pulmonary edema, skin abrasion, subintimal injection, tachypnea, and tongue swelling.

The following events occurred in one patient each in the TRUFILL™ NBCA group, and did not occur in the Onyx™ LES group: catabolic state, coagulopathy, corneal abrasion, elective carotid aneurysm surgery, high flow fistula, multi-organ system complications, myopathy/neuropathy, orthostasis, post craniotomy revision, surgical revision, transient ischemic attack (TIA), trauma, ureteral perforation, and vocal cord paralysis.

Table 17. Incidence of Complications

EVENT NAME	TRUFILL™ NBCA N=63		Onyx™ LES N=54	
	# of events	# of patients (%)	# of events	# of patients (%)
Death	0	0 (0.0%)	3	3 (5.6%)
Headache +/- nausea and vomiting	84	47 (74.6%)	74	45 (83.3%)
Patient discomfort	48	37 (58.7%)	58	39 (72.2%)
Laboratory/Imaging abnormalities	58	40 (63.5%)+	53	39 (72.2%)+
Endocrine/Metabolic	31	27 (42.9%)	29	26 (48.2%)
Hematologic	14	13 (20.6%)	13	12 (22.2%)
Asymptomatic MRI/CT Findings	6	6 (9.5%)	5	4 (7.4%)
Respiratory/Pulmonary	2	2 (3.2%)	3	3 (5.6%)
General	3	3 (4.8%)	2	2 (3.7%)
Gastrointestinal (GI)	0	0 (0%)	1	1 (1.9%)
Cardiac	1	1 (1.6%)	0	0 (0%)
Infectious/Inflammatory	1	1 (1.6%)	0	0 (0%)
Worsening Neurologic Status	40	28 (44.4%)+	43	35 (64.8%)+
Persistent	23	15 (23.8%)	22	16 (29.6%)
Resolved	17	14 (22.2%)	21	19 (35.2%)
Hyperglycemia	53	45 (71.4%)	39	35 (64.8%)
Infection	15	14 (22.2%)	16	14 (25.9%)
Bleeding and/or Low Hct requiring transfusion	17	17 (27.0%)+	15	14 (25.9%)+
Surgical Bleeding	9	9 (14.3%)	12	11 (20.4%)
Decreased Hct Requiring Transfusion	5	5 (7.9%)	3	3 (5.6%)
GI Bleeding	2	2 (3.2%)	0	0 (0%)
Other – bAVM Rupture	1	1 (1.6%)	0	0 (0%)
Intracranial Hemorrhage	13	11 (17.5%)	13	13 (24.1%)
Medication reaction	5	5 (7.9%)	11	10 (18.5%)
Failed access*	13	12 (19.0%)	9	8 (14.8%)
Access site bleeding	3	3 (4.8%)	7	4 (7.4%)
Fever	4	4 (6.3%)	7	7 (13.0%)
Delivery Catheter removal difficulty*	1	1 (1.6%)	6	5 (9.3%)
Poor penetration/ visualization*	0	0 (0%)	6	5 (9.3%)
Hypotension	0	0 (0%)	5	3 (5.6%)
Stroke	2	2 (3.2%)	4	4 (7.4%)
Cardiac arrhythmia	2	2 (3.2%)	2	2 (3.7%)
Hydrocephalus	1	1 (1.6%)	2	2 (3.7%)
SIADH (Syndrome of inappropriate antidiuretic hormone secretion, dilutional hyponatremia)	0	0 (0%)	2	2 (3.7%)
Vessel Dissection	0	0 (0%)	2	2 (3.7%)
Hypertension	3	3 (4.8%)	1	1 (1.9%)
Limb ischemia	2	1 (1.6%)	1	1 (1.9%)
Respiratory failure	4	4 (6.3%)	1	1 (1.9%)
Seizures	5	4 (6.3%)	1	1 (1.9%)
UTI (Urinary tract infection)	1	1 (1.6%)	1	1 (1.9%)
Vasospasm	5	4 (6.3%)	1	1 (1.9%)
Vaso-vagal episode	1	1 (1.6%)	1	1 (1.9%)
Cardiac arrhythmia/ hypertension	2	2 (3.2%)	0	0 (0%)
Embolization of unintended vessel*	7	6 (9.5%)	0	0 (0%)
Premature polymerization time*	3	3 (4.8%)	0	0 (0%)

Table 17. Incidence of Complications				
EVENT NAME	TRUFILL™ NBCA N=63		Onyx™ LES N=54	
	# of events	# of patients (%)	# of events	# of patients (%)
Vascular access complication	2	2 (3.2%)	0	0 (0%)
Prolonged polymerization time*	5	5 (7.9%)	0	0 (0%)
+Patients could be counted multiple times within categories so the sum of percentages within the subcategories may not equal the total for the main category. *Technical or Procedural Event only with no clinical sequelae.				

Clinical Study Conclusions

In conclusion, the clinical study has met its study hypothesis, demonstrating non inferiority of the Onyx™ LES in comparison to TRUFILL™ NBCA in the ability to occlude a bAVM prior to surgical resection. Secondary efficacy endpoint analysis shows no difference in surgical blood loss and surgical resection time between the two groups. The safety profile has been shown to be similar between the two groups.

en Symbol Glossary			
STERILE	**en** Sterilized using dry heat		**en** Non-pyrogenic
STERILE EO	**en** Sterilized using ethylene oxide		**en** Keep away from sunlight
	en Single sterile barrier system		**en** Keep dry
	en Do not re-use	REF	**en** Catalogue number
Rx ONLY	**en** Caution: Federal (USA) law restricts this device to sale by or on the order of a physician		**en** Manufacturer
STERILIZE	**en** Do not resterilize		**en** Use-by date
www.medtronic.com/manuals	**en** Consult electronic instructions for use	LOT	**en** Batch code
	en Caution		**en** Date of manufacture
	en Do not use if package is damaged and consult instructions for use	CONTENTS	**en** Contents of Package
MR	**en** MR Conditional	MD	**en** Medical device

Micro Therapeutics, Inc.
d/b/a ev3 Neurovascular
9775 Toledo Way
Irvine, CA 92618
USA
Tel: +1.949.837.3700

M016938CDOC2 Rev. G (12/2025)