TRUFILL™ n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System

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LCN 207142-001/F

Revised 2025/12

(recycle symbol)

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IMPORTANT INFORMATION
Please Read Before Use

TRUFILL™ n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System

n-Butyl Cyanoacrylate	STERILE	Sterilized using dry heat, and
	STERILE EO	Sterilized using ethylene oxide gas.
Tantalum Powder	STERILE R	Sterilized using irradiation.
Ethiodized Oil	STERILE	Sterilized using moist heat

℞ Only

Description

The TRUFILL n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System is an artificial embolization device, comprised of TRUFILL n-Butyl Cyanoacrylate (n-BCA), TRUFILL Ethiodized Oil and TRUFILL Tantalum Powder. These components must be used as a system. They are not intended for use as individual components.

The TRUFILL n-BCA Liquid Embolic System is used under fluoroscopic guidance to obstruct or reduce blood flow to embolize arteriovenous malformations (AVMs) and the Middle Meningeal Artery (MMA). Upon contact with body fluids or tissue, the mixture polymerizes into a solid material. The n-BCA is a clear, free-flowing liquid that polymerizes via an anionic mechanism. Ethiodized Oil is a straw-to-amber colored, oily fluid containing iodinated poppy seed oil and is used as a radiopaque polymerizing retardant. The amount of Ethiodized Oil used will vary the rate of polymerization. Tantalum (Ta) Powder is a finely ground, irregularly shaped, dark gray metal that can be used with Ethiodized Oil to make the n-BCA radiopaque.

The TRUFILL n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System is available in two kit configurations:

Product Code	Description
631-400	Two 1 g tubes of n-BCA, one 10 mL vial of Ethiodized Oil and one 1 g vial of Tantalum Powder
631-500	One 1 g tube of n-BCA, one 10 mL vial of Ethiodized Oil and one 1 g vial of Tantalum Powder

Indications

The TRUFILL n-BCA Liquid Embolic System is indicated for the embolization of cerebral arteriovenous malformations (AVMs) when pre-surgical devascularization is desired and for embolization of the Middle Meningeal Artery (MMA) for the treatment of symptomatic subacute and chronic Subdural Hematoma (SDH) as an adjunct to surgery.

Contraindications
Separate use of the individual components of the TRUFILL n-BCA Liquid Embolic System is contraindicated. The components must be used as a system.

Ethiodized oil alone should not be injected:
- Intravascularly
- Intrathecally
- Intrabronchially

Use of the TRUFILL n-BCA Liquid Embolic System is contraindicated when any of the following conditions exist:
- Optimal catheter placement is not possible.
- A previous history of reactions to cyanoacrylates exists.
- A previous history of hypersensitivity to Ethiodized Oil exists.
- A previous history of reactions to iodine exists.
- Provocative testing indicates intolerance to the occlusion procedure.
- Vasospasm stops blood flow.
- High blood flow precludes safe infusion of an embolic agent.

WARNINGS

- The TRUFILL n-BCA Liquid Embolic System should only be used by physicians trained in interventional endovascular procedures at medical facilities with the proper imaging equipment.
- Prior to injection it is essential to determine, via fluoroscopy, the radiopacity of the mixture by comparison with a similar syringe containing contrast. Inadequate visualization of the mixture could cause inappropriate embolization.
- The n-BCA is a fast-setting adhesive capable of adhering to most body tissues. It will polymerize in the presence of anionic media, such as body fluids or tissues. Proper handling is required to avoid premature polymerization and occlusion of the delivery system or adherence of the catheter tip to the vessel wall.
- TRUFILL Ethiodized Oil should never be used as a radiopaque contrast agent to assess hemodynamics and should be used only to prepare the TRUFILL n-BCA Liquid Embolic System.
- Do not dilute or mix TRUFILL n-BCA with any substance other than the Ethiodized Oil or Tantalum Powder included in the TRUFILL kit.
- Embolization could influence blood flow patterns, thereby subjecting arteries supplying the embolization target to increased pressures. Increased arterial pressures can result in hemorrhagic complications.
- Laboratory studies have determined that TRUFILL Ethiodized Oil can elute over time.
- Life threatening and fatal reactions can occur without warning. A fully equipped emergency cart and resuscitation equipment must be readily available at all times, along with personnel competent in recognizing and treating reactions of all severity.

Precautions
- Store in a cool, dark, dry place.
- Inspect the sterile package carefully. Do not use if:
  - the package or seal appears damaged,
  - the contents appear damaged,

- the expiry date has passed.

- The safety and performance of the TRUFILL n-BCA Liquid Embolic System has not been demonstrated in pediatric populations.
- Angiography is necessary for pre-embolization evaluation, operative control, and post-embolization follow-up.
- Verify that the n-BCA is a clear and free-flowing liquid prior to use. Do not use the product if material has thickened, discolored, or contains particulate matter. Discard and open a new TRUFILL n-BCA Liquid Embolic System.
- Use of a 21 or 23 gauge needle to aspirate the n-BCA into an appropriate injection syringe is recommended.
- The n-BCA will adhere to most surfaces. Avoid contact with non-disposable surfaces or surfaces that cannot be cleaned with acetone.
- Gloves and eye/face protection are recommended when handling n-BCA.
- Verify that the catheters and accessories used in direct contact with the system are clean and compatible with the material and do not trigger polymerization or degrade upon contact. Refer *to "Recommended Accessories"* under the "*Directions for Use*" section of these Instructions for Use.
- Do not use with any device containing polycarbonate. Cyanoacrylates cause polymers containing polycarbonate to deteriorate.
- Avoid contact with the eyes. In case of accidental contact, immediately wash with water and seek medical attention.
- Therapeutic embolization should not be performed when high blood flow precludes the safe infusion of embolic agents.
- Do not use saline or any ionic fluid when handling or mixing n-BCA to avoid premature polymerization.

Training

TRUFILL n-BCA Liquid Embolic System should only be used by physicians trained in interventional endovascular procedures at medical facilities with the proper imaging equipment.

Potential Adverse Events

Potential adverse events associated with embolization procedures can occur at any time during or after the procedure. These include, but are not limited to:

- Access site injury (including bleeding, bruising, infection, pain)
- Allergic reaction/anaphylactic shock
- Catheter glued inside vessel (catheter entrapment)
- Cerebral infarction
- Death
- Early polymerization
- Embolism, including pulmonary and thromboembolism
- Headache
- Hematoma
- Hemorrhage
- Infection/inflammation
- Late polymerization
- Myocardial infarction

- Nausea/vomiting
- Neurological deficits
- Non-target embolization (passage of embolic material into normal vessels adjacent to the target) which may cause but not limited to blindness, dysesthesias of the face (increased or decreased sensitivity), facial weakness, or deafness
- Occluded catheter
- Renal failure
- Seizure
- Stroke
- Subdural hematoma recurrence
- Vasospasm
- Vessel dissection, perforation, and injury

Use of device requires fluoroscopy which presents potential risks to physicians and patients associated with x-ray exposure. Possible risks include, but are not limited to, the following:

- Alopecia
- Burns ranging in severity from skin reddening to ulcers
- Cataracts
- Delayed neoplasia

How Supplied

This product is for SINGLE USE ONLY; DO NOT RESTERILIZE. Cerenovus will not be responsible for product that is resterilized, nor accept for credit or exchange product that has been opened but not used.

As long as the inner unit is not opened or damaged, the TRUFILL n-BCA Liquid Embolic System is sterile and nonpyrogenic.

Storage and Handling

Remove the components from the carton just prior to use. Protect the Ethiodized Oil from light.

Magnetic Resonance Imaging (MRI) Safety Information

MR Conditional 

MRI Safety Information

A person with the TRUFILL n-BCA Liquid Embolic System and Procedural Set may be safely scanned under the following conditions. Failure to follow these conditions may result in injury.

Device Name	TRUFILL n-BCA Liquid Embolic System and Procedural Set
Static Magnetic Field Strength (Bo)	1.5 T or 3.0 T
Maximum Spatial Field Gradient	40 T/m (4,000 gauss/cm)
RF Excitation	Circularly Polarized (CP)
RF Transmit Coil Type	There are no Transmit Coil restrictions
RF Receive Coil Type	Any
Operating Mode	Normal Operating Mode
Maximum Whole-Body SAR	2 W/kg (Normal Operating Mode)
Maximum Head SAR	3.2 W/kg (Normal Operating Mode)
Scan Duration	2 W/kg whole-body averaged SAR for 60 minutes of continuous RF (a sequence or back to back series/scan without breaks)
MR Image Artifact	The presence of this implant may produce an image artifact of up to 8 mm.

Directions for Use

Recommended Accessories

CAUTION: Do not use with syringes containing polycarbonate. Verify syringe material before use.

- The TRUFILL n-BCA Liquid Embolic System is designed and tested to be delivered under fluoroscopy through the PROWLER™ and TRANSIT™ families of microcatheters. Use with any other catheter has not been evaluated.
- The n-BCA, Ethiodized Oil, and Tantalum Powder (if used) mixture should be prepared using a 1mL to 10 mL syringe (made of polyethylene or polypropylene).
- To inject the mixture through the infusion catheter, a 1 mL to 3 mL syringe with Luer lock made of polyethylene or polypropylene is recommended.
- A 21 or 23 gauge needle is recommended to aspirate and/or transfer the n-BCA, the Ethiodized Oil and the mixture.
- A sterile 25 mL to 50 mL glass beaker or equivalent is recommended for preparation of the mixture.

Pre-Embolization

TRUFILL n-BCA Liquid Embolic System should only be used by physicians trained in interventional endovascular procedures at medical facilities with the proper imaging equipment.

Serious, including fatal, consequences can result with the use of the TRUFILL n-BCA Liquid Embolic System without adequate training. Contact your Johnson and Johnson Medtech Neurovascular sales representative for information on training courses.

Prior to use, perform baseline angiography to determine the vascular supply to the lesion. Note: For treatment of AVMs, the angiogram should demonstrate the route of the catheter entry as well as identify relevant collateral circulation.

1. Introduce the infusion catheter according to standard technique. Position the infusion catheter as close as possible to the treatment site to avoid inadvertent occlusion of normal vessels.

2. Perform contrast injections to assess hemodynamics prior to embolization.

CAUTION: **The Ethiodized Oil must not be used as a radiopaque contrast agent to assess hemodynamics and must be used only to prepare the n-BCA mixture. Ethiodized Oil is contraindicated for intravascular, intrathecal or intrabronchial use.**

Recommended Mixtures

1. Radiopacity of the n-BCA mixture is accomplished by adding Ethiodized Oil and Tantalum Powder to the n-BCA. These additives will also extend the polymerization time of the n-BCA.

2. Recommended ratios of n-BCA to Ethiodized Oil and Tantalum Powder vary depending on the location of injection and flow rates.

CAUTION: **Therapeutic embolization should not be performed when high blood flow precludes the safe infusion of embolic agent.** Higher concentrations of Ethiodized Oil increase the polymerization time, which allows for more distal penetration. Higher concentrations of n-BCA result in a faster polymerization rate, which will allow the physician to embolize the vasculature more proximally. Ratios used in the prospective, randomized clinical study of the TRUFILL n-BCA Liquid Embolic System varied from 10% to 70% n-BCA and 30% to 80% Ethiodized Oil by volume. Refer to Figure 1 for polymerization rates at various ratios. Ratios outside these parameters have not been tested clinically and are not recommended. Guidelines are recommended in Table 4.

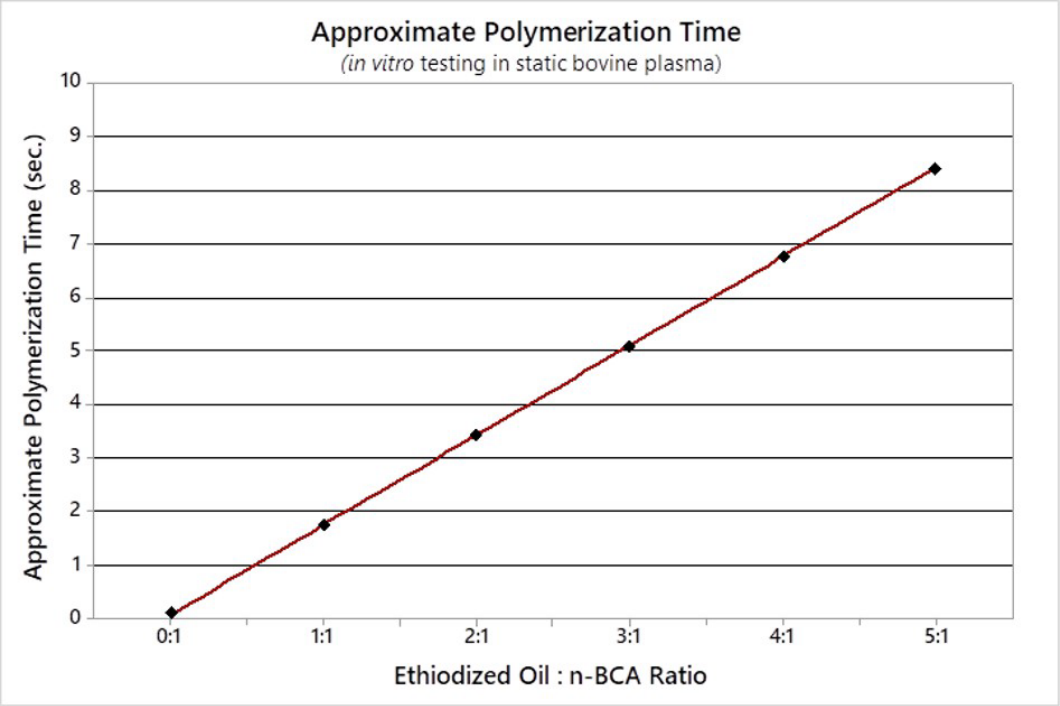


Figure 1

Preparation of Mixture

1. Snap the top off the neck of the Ethiodized Oil vial using a sterile alcohol wipe.

2. Put the desired amount of Ethiodized Oil and, if using, Tantalum Powder into a clean, sterile glass beaker. Mixing can be achieved by aspirating in and out of a syringe until the mixture appears homogenous.

CAUTION: Thoroughly mix the radiopacity agents prior to adding the **n-BCA. Do not use Tantalum Powder alone with n-BCA.**

3. To remove the TRUFILL n-BCA from the tube, attach the self-piercing cap to a Luer lock syringe and then attach the other end of the cap (with the syringe connected to it) to the n-BCA tube. While screwing the cap onto the tube you will first feel resistance which will ease when the seal of the tube is punctured. Continue twisting the cap onto the tube until resistance builds again, signaling a proper seal between the syringe, cap, and tube. Avoid spilling the n-BCA, by keeping the tube crimped side down and the cap with syringe up until a proper seal is achieved. To withdraw the n-BCA, turn the syringe-cap-tube assembly to the tube crimped side up and extract the desired amount of n-BCA into the syringe.

4. Inspect the n-BCA to verify that it is clear and free flowing. Do not use any material that is thickened, discolored, or contains particulate matter prior to use. Discard and open a new TRUFILL n-BCA Liquid Embolic System.

5. Add the desired amount of n-BCA to the sterile glass beaker. Mix thoroughly as described above until the mixture appears homogenous.

WARNING: Polymerization time, viscosity, and injection technique are interrelated and affect the progress of embolization. The appropriate formulation of any additives is dependent upon the expert evaluation of the relationship of anatomy, hemodynamics, and the catheter system. Figure 1 illustrates the polymerization rates obtained during in vitro testing in static bovine plasma.

WARNING: A 0:1 Ethiodized Oil to n-BCA ratio should never be used. Refer to the *"Recommended Mixtures"* section and Figure 1 for recommended ratios.

6. To determine whether your mixture is sufficiently radiopaque for visualization, compare it under fluoroscopy to a similar syringe full of contrast media.

Injection of Mixture

1. Aspirate the mixture into an appropriate injection syringe through a 21- or 23-gauge needle to verify that no material is agglomerated. Verify that the mixture is well suspended and free of air bubbles.

2. Prepare the microcatheter by thoroughly rinsing the outside of the catheter hub and flushing the catheter with a 5% dextrose solution in water.

Note: Do not rinse the glass beaker and/or the syringes with 5% dextrose prior to use. Prolonged contact of n-BCA with 5% dextrose could initiate the polymerization process.

3. Positioning the syringe tip slightly upwards (this will minimize the potential for agglomerated tantalum to obstruct the catheter lumen), inject the mixture through the microcatheter, using hand control and high-resolution fluoroscopic monitoring.

WARNING: If resistance is met during injection, do not attempt to clear or overcome the resistance by applying increased pressure. If this occurs, determine the cause of resistance and remove the catheter, if necessary. Applying increased pressure could result in rupture of the catheter and deposition of the mixture in an undesired area.

4. After injection is completed, immediately aspirate with the injection syringe and rapidly withdraw the catheter to prevent adherence of the catheter tip and to ensure that no unpolymerized mixture will leak during catheter withdrawal.

Note: If the microcatheter tip becomes glued to the vascular site, it may be necessary to seek surgical intervention.

5. Following each injection, discard the microcatheter.

6. Discard any opened and unused n-BCA, Ethiodized Oil, and Tantalum Powder.

Information to be supplied to the patient

After surgery, surgeons are to provide the patient with the Patient ID Card with information on the implant(s) used. Patients should be advised to carry the patient implant card to facilitate medical care in case of emergency.

Patient Information

Your doctor has implanted the Cerenovus TRUFILL n-BCA Liquid Embolic System.

Device Description

The TRUFILL n-BCA Liquid Embolic System is an artificial device used by doctors to block or decrease blood flow to treat abnormal blood vessels in the head.

Device Materials

TRUFILL n-BCA Liquid Embolic System is made up of three parts:

1. n-BCA: A glue that hardens to reduce blood flow. Contains:
n-Butyl Cyanoacrylate (n-BCA) 99.0%n-Butyl Cyanoacetate; Sulfur Dioxide; Butylated Hydroxyanisole

It is mixed with:

2 Ethiodized Oil: Used to control the n-BCA hardening rate. Contains: Ethyl esters of iodized fatty acids of poppy seed oil.

It can also be mixed with:

3. Tantalum Powder: A finely ground, dark gray metal. This allows the device to be seen on X-ray. Contains:
Tantalum

Tell your doctor before surgery about any allergies you have to cyanoacrylates, ethiodized oil or iodine.

Information for Safe Use
Make sure to follow your doctors' orders for general safety.
Magnetic Resonance Imaging (MRI) is a test used to diagnose certain diseases.
Also, it can be used during medical procedures.
Before having an MRI, tell your doctors if you have an implanted medical device. **You can provide this document to your doctors so that they have the necessary information for performing a safe MRI.**

MRI Safety Information

A person with the TRUFILL n-BCA Liquid Embolic System and Procedural Set may be safely scanned under the following conditions. Failure to follow these conditions may result in injury.

Device Name	TRUFILL n-BCA Liquid Embolic System and Procedural Set
Static Magnetic Field Strength (Bo)	1.5 T or 3.0 T
Maximum Spatial Field Gradient	40 T/m (4,000 gauss/cm)
RF Excitation	Circularly Polarized (CP)
RF Transmit Coil Type	There are no Transmit Coil restrictions
RF Receive Coil Type	Any
Operating Mode	Normal Operating Mode
Maximum Whole-Body SAR	2 W/kg (Normal Operating Mode)
Maximum Head SAR	3.2 W/kg (Normal Operating Mode)
Scan Duration	2 W/kg whole-body averaged SAR for 60 minutes of continuous RF (a sequence or back to back series/scan without breaks)
MR Image Artifact	The presence of this implant may produce an image artifact of up to 8 mm.

Patient Information Portal

Any updated information will be provided on our website, ic.jnjmedicaldevices.com.

Information specific to your implant, including the serial number, unique device identifier, etc. are included on the implant card as well as in patient records kept by

your healthcare provider.

Clinical Trials

TRUFILL n-BCA Clinical Trial for treatment of cerebral AVMs

Study Design

A prospective, multi-center, single-blind, randomized study was conducted to determine whether the TRUFILL n-BCA Liquid Embolic System was as safe and effective as poly-vinyl alcohol (PVA) for use in the obliteration of cerebral AVMs when pre-surgical devascularization is desired. The primary effectiveness outcome was the degree of vascular occlusion (percent nidus/lesion reduction and number of vessels occluded) as determined by the angiographic core laboratory. Secondary effectiveness outcomes were the length of time to resect the AVM and the number of transfusions required/total blood loss during the surgery. Primary safety outcomes for comparison to control treatment were the incidences of device-related complications, procedural complications, intracranial events, and unanticipated adverse device effects. Other safety measures, clinical neurological examinations, Glasgow Outcome Scores, and NIH Stroke Scale scores, were summarized at each of the follow-up time periods: post procedure, pre surgery, and post-surgery. Patients enrolled in the study were those who had an AVM that required preoperative devascularization as determined angiographically. Patients with Spetzler-Martin grade III, IV and V AVMs were treated. Patients with grade I and II lesions were treated if the anticipated benefit of the embolization was greater than the risk of the embolization procedure, and if the AVM feeding pedicle was located in an area that was difficult to surgically access. Conjunctive therapy using coils was permitted prior to embolization to slow the flow rate (if needed) or if a portion of the AVM contained blood vessels that were larger than the largest size of PVA available. Patients who had been previously embolized with PVA or cyanoacrylate and patients with a known sensitivity to iodine containing contrast reagents were excluded from the study.

Patient Accounting

A total of 104 patients were enrolled into the study, 52 patients were randomized into each treatment group. Three patients of the PVA group were determined not able to be evaluated for the effectiveness analysis. Two crossover patients were randomized to PVA but were treated with n-BCA and one PVA patient was not used for effectiveness analyses due to inadequate source documentation. Four n-BCA patients were not embolized and therefore not included in the effectiveness analyses. Two patients were not embolized due to an inability to subselect the feeder vessel. One patient was not embolized because the physician deemed the location and type of AVM too dangerous to embolize. Finally, one patient was embolized with coils at Stage 1 and was to receive n-BCA during Stage 2 but withdrew consent.

Therefore, the total number of patients who were included in the primary effectiveness outcome analysis was 97; 48 patients in the n-BCA group and 49 patients in the PVA group. The safety data set included 54 n-BCA and 52 PVA patients. Two patients who were randomized to PVA, but who received n-BCA after failed attempts to effectively embolize with PVA, have their complications listed (n-BCA or PVA) by when they occurred, i.e., during embolization or during surgical resection. Four of the five complications these patients experienced occurred during the PVA embolization stage and therefore are listed as PVA complications. One complication (other – considerable bleeding) occurred during resection after n-BCA embolization and, therefore, is listed as an n-BCA complication.

Methods

Preembolization and postembolization angiograms were obtained to determine the extent of occlusion achieved. The angiograms were sent to the angiographic core laboratory where anterior/posterior (AP) and lateral views of the nidus and selective arteriograms of the selected feeding pedicles were evaluated.

Adverse Events

A total of 104 patients (52 TRUFILL n-BCA Liquid Embolic System, 52 poly-vinyl alcohol (PVA) (control)) were enrolled for safety evaluation in a clinical trial for the treatment of cerebral AVMs. Two patients who were randomized to PVA, but who received n-BCA after failed attempts to effectively embolize with PVA, have their complications listed (n-BCA or PVA) by when they occurred, i.e., during embolization or during surgical resection. Four of the five complications these patients experienced occurred during the PVA embolization stage and therefore are listed as PVA complications. One complication (other – considerable bleeding) occurred during resection after n-BCA embolization and, therefore, is listed as an n-BCA complication. Therefore, the number of patients used for calculation of the incidence of adverse events in the n-BCA group is 54. Fifty-two percent of the patients in the n-BCA group and 54% of the patients in the PVA group (n-BCA: 51.9%, N = 28, and PVA: 53.9%, N = 28) had at least one complication. There was one unanticipated adverse device event (UADE) reported for a patient in the n-BCA group during the study, described in Table 1. Two patients died during the treatment period; one due to cerebellar hemorrhage (n-BCA) and the other due to intracerebral hemorrhage (PVA), and 2 patients (PVA) died post-resection. The treatment period was defined as from pre-surgical embolization up through surgical resection. All reported adverse events that occurred in the n-BCA System cohort in the pivotal clinical study are listed in Table 1. The adverse events are listed in descending order according to frequency as observed for the study treatment group.

Adverse events associated with embolization procedures (including those observed during the clinical study), can occur at any time during or after the procedure. These adverse events include (in alphabetical order): allergic reaction, AVM rupture, catheter glued inside vessel, death, early polymerization, headache, hemorrhage, infection/inflammation, late polymerization, neurological deficits, occluded catheter, passage of embolic material into normal vessels adjacent to the lesion, pulmonary embolism, seizure, stroke or cerebral infarction, thromboembolism, vasospasm, vessel dissection, and vessel perforation.

Primary Effectiveness Results

The primary effectiveness outcome was the degree of vascular occlusion (percent nidus/lesion reduction and number of vessels occluded). Staged embolizations (more than one embolization procedure per patient) were allowed. The mean percent reduction in lesion volume and the mean number of feeding vessels occluded per patient and per stage are listed in Table 2.

Secondary Effectiveness/Safety Results

Additional parameters assessed included the time of resection and the blood volume replacement needed (units of blood, fluid/colloid, or amount from autologous blood recovery device.) Results for the time of resection and blood volume replacement are reported in Table 3.

Table 1
Incidence of Complications

Complications	**n-BCA (N=54)**	**PVA (N=52)**
Seizure	5 (9.3%)	5 (9.6%)
Catheter glued inside vessel	4 (7.4%)	0 (0.0%)
Late Polymerization	3 (5.6%)	0 (0.0%)
Occluded Catheter	3 (5.6%)	5 (9.6%)
Parenchymal hemorrhage	3 (5.6%)	6 (11.5%)
Vasospasm	3 (5.6%)	7 (13.5%)
AVM rupture	2 (3.7%)	1 (1.9%)
Early Polymerization	2 (3.7%)	0 (0.0%)
Inability to subselect vessel	2 (3.7%)	4 (7.7%)
CVA (stroke)	2 (3.7%)*	3 (5.8%)
Death	1 (1.9%)	3 (5.8%)
Hematoma	1 (1.9%)	1 (1.9%)
Incorrect vessel(s) occluded	1 (1.9%)*	0 (0.0%)
Infection/Inflammation	1 (1.9%)	0 (0.0%)
Over-the-wire system could not be advanced	1 (1.9%)	1 (1.9%)
Thromboembolism	1 (1.9%)	1 (1.9%)
Vessel dissection	1 (1.9%)	1 (1.9%)
Vessel perforation	1 (1.9%)	3 (5.8%)
Cranial ischemia (TIA)	0 (0.0%)	2 (3.8%)
Catheter rupture	0 (0.0%)	1 (1.9%)
Failure to access vessel	0 (0.0%)	2 (3.8%)
Flow too high for safe infusion of embolic agent	0 (0.0%)	2 (3.8%)
Headache	0 (0.0%)	2 (3.8%)
Pulmonary embolism	0 (0.0%)	1 (1.9%)
Subarachnoid hemorrhage	0 (0.0%)	2 (3.8%)
Subject failed provocative test	0 (0.0%)	1 (1.9%)
Subject uncooperative	0 (0.0%)	2 (3.8%)
Other	9 (17.3%)*	9 (17.3%)

**One patient (n-BCA) was discontinued from the clinical trial due to an unanticipated adverse device effect. A small amount of glue refluxed into the proximal middle cerebral artery and embolized into branches of the middle cerebral artery. The patient developed a neurologic deficit with aphasia and hemiparesis. This event resulted in permanent disability and the patient was determined not to be an appropriate surgical candidate due to neurological status.*

Table 2
Lesion Volume Reduction and Feeder Vessel Occlusion per Patient and per Stage, by Treatment

	Patient		Stage	
	n-BCA	PVA	n-BCA	PVA
Mean Percent Reduction In Lesion Volume	79.4 (N=47)	86.9 (N=47)	81.1 (N=71)	79.9 (N=76)
Mean Number of Feeding Vessels Occluded	2.2 (N=48)	2.1 (N=45)	1.5 (N=72)	1.3 (N=72)

The value of N provided in parentheses represents the number of patients or stages without missing data that were used for the effectiveness analyses.

Table 3
Summary of Data During Surgery – Time to Resect AVM and Volume Blood Replacement Needed

	n-BCA[1](N=52)	PVA[2] (N=49)	Total (N=101)
Was AVM resected?			
Yes	49 (92.5%)	48 (92.3%)	97 (92.4%)
No[3]	4 (7.5%)	4 (7.7%)	8 (7.6%)
Time to resect AVM (min.)			
N	47	46	93
Mean	393.9	401.3	397.5
Median	373.0	357.5	365.0
Volume Replacement Needed: Units of blood or blood product			
N	47	44	91
Mean	1.1	3.1	2.0
Volume Replacement Needed: Fluid/colloid (mL)			
N	47	47	94
Mean	3683	3597	3640
Volume Replacement Needed: Amount from autologous blood recovery device (mL)			
N	41	40	81
Mean	48.8	181.8	114.4

[1]One n-BCA patient underwent multiple resections.
[2]Two PVA patients underwent multiple resections. One patient had an aborted resection after the dura was opened, then underwent true resection at a later date.
[3] One crossover patient (PVA to n-BCA) was not resected.
Note: Column headings show number of patients; however, percentages are based on total number of procedures, a total of 105 (53 n-BCA and 52 PVA).

Table 4
Recommended Mixtures (Listed volumes based on a total volume of 1.0 mL—actual total volumes may vary)

Conditions	TRUFILL Ethiodized Oil: n-BCA Ratio (EO: n-BCA)	TRUFILL Ethiodized Oil Volume (mL)	TRUFILL n-BCA Volume (mL)
Intranidal injections without AV fistulae or high flow rates, in order to more deeply penetrate the nidus	3:1 (75% EO/25% n-BCA)	0.75	0.25
	2:1 (67% EO/33% n-BCA)	0.67	0.33
Feeding pedicle injections close to the nidus, at high flow rates where venous opacification occurs on contrast injections within 0.5 second	1:1 (50% EO/50% n-BCA	0.50	0.50*
	1:2 (33% EO/67% n-BCA	0.33	0.67*
	*TRUFILL Tantalum Powder may also be added to Ethiodized Oil to augment radiopacity. Tantalum Powder should not be used alone with n-BCA. At higher n-BCA concentrations (>50%), addition of up to 0.5 g tantalum powder is advised.		

Subdural hematoma clinical trial

Note: The clinical data presented include patients enrolled in both surgical and non-surgical cohorts per the approved clinical protocol. Data from both cohorts were used to support the overall clinical evaluation. The approved indication is embolization of the Middle Meningeal Artery (MMA) for the treatment of symptomatic subacute or chronic Subdural Hematoma (SDH) as an adjunct to surgery.

Study Design

The study is titled "Middle Meningeal Artery EMbolization for the Treatment of SuBduRal HemAtomas with TRUFILL n-BCA" (MEMBRANE).

The objective of this study was to evaluate the safety and effectiveness of TRUFILL n-BCA for embolization of the Middle Meningeal Artery (MMAE) in patients presenting with a subacute or chronic Subdural Hematoma (SDH) compared to patients treated with standard of care. This study was a prospective, multi-center, open label, randomized controlled study that enrolled 376 adults at 33 sites in the US and China.

The study stratified enrollment by patients that were treated with surgery, with and without adjunctive embolization (surgical cohort), and those that were treated with non-surgical medical management (NSMM), with and without adjunctive embolization (non-surgical cohort). Data from the two cohorts were pooled and used in support of approval of the device as an adjunct to surgery.

The control group received standard of care (SOC) treatment consisting of either surgical management alone (burr hole evacuation, craniotomy, or other surgical procedures) for the surgical cohort, or NSMM alone (medication management, observation, lifestyle modifications) for the non-surgical cohort. The test group received SOC treatment (surgery or NSMM) in addition to MMAE with the TRUFILL n-BCA LES. Patients in the surgical cohort who were randomized to the test arm underwent MMAE within 10 days after the surgical procedure and within the same hospital admission. Crossover was not permitted between the randomized arms, or between the surgical cohort and the observational cohort.

Subjects were followed procedurally and at 1 month, 3 months, 6 months, and 1 year post-procedure.

Patients presenting with a SDH were assessed by the institution's neurological team to determine the appropriate SOC treatment regardless of the research study, either surgical or non-surgical medical management. Patients were then screened for trial enrollment based on the protocol inclusion and exclusion criteria. Patients who met all eligibility criteria and consented to participate in the MEMBRANE study were randomized 1:1 to undergo MMAE plus SOC vs SOC alone (either surgical or non-surgical management). Patients in the surgical cohort who were randomized to the test arm underwent MMAE within 10 days after the surgical procedure and within the same hospital admission. Crossover was not permitted between the randomized arms, or between the surgical cohort and the observational cohort.

The primary effectiveness endpoint was residual or re-accumulation of the SDH (>10 mm) at 6 months as assessed by an Independent Core Laboratory or re-operation or surgical

procedure on the SDH within 6 months post-randomization. The primary endpoint was evaluated as a superiority analysis of the test group (MMAE + SOC) to the control group (SOC alone). The endpoint was evaluated at a one-sided significance level of 0.05 using a Cochran-Mantel-Haenszel (CMH) common odds ratio.

The primary safety endpoint was occurrence of all AEs through 6 months which was evaluated descriptively.

The protocol pre-specified three hypothesis-driven secondary endpoints which were to be conducted hierarchically pending a successful primary endpoint outcome and pending success of the prior hierarchy level. The first hypothesis-driven secondary endpoint was good functional outcome at 3 months (mRS 0-2 or no worsening from baseline if baseline mRS ≥3). The second and third hypothesis-driven secondary endpoints included incidence of patients requiring surgical procedures on the SDH within 12 months and mean change in hematoma volume at 12 months with respect to baseline. Data from the second and third hypothesis driven secondary endpoints were not available at the time of labeling generation and therefore are not presented herein.

Key Inclusion Criteria

- Age 18 – 90 years at time of consent.
- Diagnosis of chronic subdural hematoma with mass effect
- Pre-randomization modified Rankin Scale (mRS) ≤ 3.
- Subdural Hematoma Size:
  Non-Surgical Medical Management Cohort:
  - Midline shift < 10 mm and hematoma thickness > 10 mm as measured on coronal image perpendicular to the skull.
  - No focal deficit related to the SDH.

  Surgical Cohort – no requirement.
- CT performed within 36 hours prior to randomization demonstrates stability of hematoma. Stability is defined as no worsening of midline shift or increase in SDH size from screening image that results in new or worsening clinical symptoms.
- In the opinion of the treating physician, treatment with TRUFILL n-BCA is technically feasible (e.g., no significant vessel tortuosity, stenosis, occlusion, variation in vascular anatomy to prohibit safe endovascular access.)
- Patient or Legal Authorized Representative confirmed the subject has the mental capacity, willingness and ability to comply with protocol and follow-up requirements.

Key Exclusion Criteria

- Acute SDH, e.g., patient with a SDH due to trauma (mixed density is permitted).
- History of craniotomy/burr hole/Subdural Evacuation Port System (SEPS) ipsilateral to SDH prior to the baseline procedure treatment.

- Bilateral SDH (contralateral SDH <5mm and not requiring treatment permitted)
- Glasgow Coma Scale (GCS) < 9.
- Markwalder Grading Scale (MGS) assessment ≥ 3.
- SDH with underlying conditions such as vascular lesions, brain tumor, arachnoid cyst, spontaneous intracranial hypotension, end stage renal disease on hemodialysis, end stage liver disease, or other comorbidities causing coagulopathy.
- Prior carotid stent placement that crosses the origin of the External Carotid Artery (ECA) ipsilateral to the subdural hematoma.
- Selective angiography demonstrates opacification of a potentially dangerous anastomosis or dangerous anatomic variation that could lead to increased procedural risk.
- Life expectancy of less than 1 year.
- Presumed septic embolus, or suspicion of microbial superinfection.
- CT or MRI evidence of intra-cranial tumor or mass lesion.
- Significant contraindication to angiography (e.g., kidney failure).
- Women who were pregnant, lactating, or who were of childbearing age and planned on becoming pregnant during the course of the clinical investigation.
- Current involvement in an investigational (drug, device, etc.) clinical trial that may have confounded study endpoints; subjects in observational, natural history, and/or epidemiological studies not involving intervention were eligible; Sponsor approval was required prior to randomization.
- Subject unwilling to follow SOC recommendations (e.g., refused surgery or lifestyle modifications).

Patient Accounting

At the time of database lock, 390 patients enrolled in the MEMBRANE study of which 376 subjects were randomized including 188 test subjects (133 MMAE + surgery, 55 MMAE + NSMM) and 188 control subjects (132 surgery alone, 56 NSMM alone). Of the subjects that were consented but not randomized, 11 failed to meet eligibility criteria and 3 withdrew prior to randomization. The following analysis populations were defined and used in the protocol:

Intent-to-Treat (ITT) Analysis Set: This set includes all enrolled subjects who were randomized in the study. Subjects were analyzed as randomized regardless of treatment received.

Per Protocol (PP) Analysis Set: This set is a subset of the ITT analysis set, excluding the subjects with significant eligibility deviations, as well as those who did not receive treatment as assigned, in addition to other major protocol deviations which were outlined in the SAP.

As Treated (AT) Analysis Set: This set includes all subjects randomized in the study who received study treatment. Subjects were analyzed by actual treatment they received.

Of the enrolled subjects, 303 subjects completed the 6-month visit and 277 (73.7%) patients had primary endpoint data at the 6-month post-operative visit.

Reasons for not completing the 6-month visit were death prior to completion of 6-month visit in 22 subjects (5.9%), withdrawal by subject in 21 (5.6%), relocation in 1 (0.3%), whereas 29 (7.7%) were ongoing but did not perform a 6-month visit.

Additionally, 8 subjects in the test arm (4 in the surgical cohort and 4 in the non-surgical cohort) did not receive the TRUFILL LES. In the control arm, 15 subjects did not receive their assigned treatment (9 in the surgical cohort and 6 in the non-surgical cohort).

Demographics

Demographic characteristics for subjects in the MEMBRANE clinical trial are summarized in Table 5.

Table 5
Demographics and Baseline Characteristics

Category	TRUFILL+SOC N=188	SOC Alone N=188
Age at consent (years), Mean (Standard Deviation)	70.9 (10.64)	70.3 (12.05)
Gender, Female, n/N* (%)	45/188 (23.9)	49/188 (26.1)
Ethnicity, n/N* (%)		
Hispanic or Latino	15/188 (8.0)	11/188 (5.9)
Not Hispanic or Latino	171/188 (91.0)	173/188 (92.0)
Not reported	2/188 (1.1)	4/188 (2.1)
Race, n/N* (%)		
American Indian or Alaska Native	0/188 (0.0)	1/188 (0.5)
Asian	18/188 (9.6)	17/188 (9.0)
Black or African American	29/188 (15.4)	26/188 (13.8)
Native Hawaiian or other Pacific Islander	0/188 (0.0)	0/188 (0.0)
White	124/188 (66.0)	128/188 (68.1)
Not Reported	15/188 (8.0)	16/188 (8.5)
Other	2/188 (1.1)	0/188 (0.0)
Multi-racial	0/188 (0.0)	0/188 (0.0)
Modified Rankin Score (mRS), n/N* (%)		
0-2	141/188 (75.0)	145/188 (77.1)
3	47/188 (25.0)	43/188 (22.9)
Hypertension, n/N (%)	124/188 (66.0)	138/188 (73.4)
Current Smoker, n/N (%)	22/188 (11.7)	18/188 (9.6)
Chronic Alcoholism, n/N (%)	24/188 (12.8)	19/188 (10.1)
Prior ischemic stroke, n/N (%)	20/188 (10.6)	14/188 (7.4)
Antiplatelet and/or Anticoagulant Medication at Symptom Onset[1], n/N (%)		
Antiplatelet Medication Only	3/188 (1.6)	8/188 (4.3)
Anticoagulant Medication Only	68/188 (36.2)	34/188 (18.1)
Antiplatelet and Anticoagulant Medication	2/188 (1.1)	4/188 (2.1)

n = number of subjects with data available by category; N = number of subjects in the analysis set.
Note: Denominator (N) of the percentage is based on the number of subjects with non-missing values.*
Note: Denominator (N) of the percentage is based on the number of subjects in the analysis set.
[1]Antiplatelet and/or anticoagulant medications that were taken at the time of randomization (medication start date on or prior to the randomization date and medication end date on or after the randomization date).

Baseline Chronic Subdural Hematoma Characteristics

Baseline SDH characteristics per Independent Core Lab for subjects in the MEMBRANE clinical trial are summarized in Table 6.

Table 6
Target Chronic Subdural Hematoma Baseline Characteristics

Category	TRUFILL+SOC N=188	SOC Alone N=188
Presence of an acute component, n/N (%)	160/187 (85.6)	157/185 (84.9)
Anatomic side of SDH, n/N* (%)		
Bilateral	20/188 (10.6)	27/188 (14.4)
Unilateral	168/188 (89.4)	161/188 (85.6)
Volume of hematoma (cm3), Mean (Standard Deviation)	69.95 (41.083)	76.47 (43.542)
Thickness of hematoma (mm), Mean (Standard Deviation)	15.19 (5.097)	15.06 (5.110)
Midline shift (mm), Mean (Standard Deviation)	4.70(3.311)	4.51 (2.879)
Headache, n/N (%)	122/188 (64.9)	128/188 (68.1)
Memory Loss or Confusion, n/N (%)	77/188 (41.0)	75/188 (39.9)
Dysarthria or Aphasia, n/N (%)	53/188 (28.2)	40/188 (21.3)
Gait Impairment / Instability, n/N (%)	79/188 (42.0)	86/188 (45.7)
Limb Weakness, n/N (%)	90/188 (47.9)	91/188 (48.4)
Baseline MGS, Mean (Standard Deviation)	1.0 (0.63)	1.0 (0.65)
Baseline mRS, Mean (Standard Deviation)	1.59 (1.038)	1.55 (0.982)

n = number of subjects with data available by category; N = number of subjects in the analysis set.
Note: Denominator (N) of the percentage is based on the number of subjects with non-missing values.*
Note: Denominator (N) of the percentage is based on the number of subjects in the analysis set.

Treatment and Procedural Details

Treatment and procedural details for subjects in the MEMBRANE clinical trial are summarized in Table 7.

Table 7
Treatment and Procedural Details

Category	TRUFILL+ Surgery N=133	TRUFILL + NSMM N=55
Side treated, n/N* (%)		
Left	60/133 (45.1)	22/55 (40.0)
Right	58/133 (43.6)	29/55 (52.7)
Bilateral	15/133 (11.3)	4/55 (7.3)
MMAE Procedural time (minutes), Mean (Standard Deviation)	71.1 (31.99)	71.5 (33.65)
Surgical Procedure type, n/N* (%)		
Craniotomy	47/133 (35.3)	Not applicable
Burr-hole Evacuation	95/133 (71.4)	Not applicable
Vascular access, n/N* (%)		
Radial artery	56/129 (43.4)	26/51 (51.0)
Femoral artery	73/129 (56.6)	25/51 (49.0)

n = number of subjects with data available by category; N = number of subjects in the analysis set.
Note: Denominator (N) of the percentage is based on the number of subjects with non-missing values.*

Adverse Events

Table 8 lists site reported adverse events in the AT analysis set through 6-month follow-up with > 1% overall frequency in either treatment arm for adverse events in the System Organ Class of “Nervous system disorders” and > 1% overall frequency in the embolization treatment groups only for adverse events in all other system organ classes.

Table 8
Summary of Adverse Events (AEs) for MEMBRANE Clinical Study by Medical Dictionary for Regulatory Activities (MedDRA) Codes

	TRUFILL+SOC N=181	SOC Alone N=190
System Organ Class (SOC) Preferred Term (PT)	**Number of subjects n/N (%)**	**Number of subjects n/N (%)**
Nervous system disorders		
Headache	23/181 (12.7)	15/190 (7.9)
Dizziness	11/181 (6.1)	5/190 (2.6)
Seizure	9/181 (5.0)	4/190 (2.1)
Partial seizures	4/181 (2.2)	3/190 (1.6)
Aphasia	3/181 (1.7)	3/190 (1.6)
Dysarthria	3/181 (1.7)	0/190 (0.0)
Hypoaesthesia	3/181 (1.7)	4/190 (2.1)
Amnesia	2/181 (1.1)	2/190 (1.1)
Cerebral infarction	2/181 (1.1)	3/190 (1.6)
Generalised tonic-clonic seizure	2/181 (1.1)	0/190 (0.0)
Metabolic encephalopathy	2/181 (1.1)	0/190 (0.0)
Tremor	2/181 (1.1)	1/190 (0.5)
VIth nerve paralysis	2/181 (1.1)	0/190 (0.0)
Encephalopathy	1/181 (0.6)	4/190 (2.1)
Facial paralysis	1/181 (0.6)	2/190 (1.1)
Lethargy	1/181 (0.6)	2/190 (1.1)
Head discomfort	0/181 (0.0)	2/190 (1.1)
Infections and infestations		
Urinary tract infection	14/181 (7.7)	8/190 (4.2)
COVID-19	11/181 (6.1)	10/190 (5.3)
Pneumonia	3/181 (1.7)	5/190 (2.6)
Diverticulitis	2/181 (1.1)	0/190 (0.0)
Septic shock	2/181 (1.1)	0/190 (0.0)
Injury, poisoning and procedural complications		
Subdural haematoma	11/181 (6.1)	23/190 (12.1)
Fall	5/181 (2.8)	5/190 (2.6)
Buttock injury	2/181 (1.1)	1/190 (0.5)
Head injury	2/181 (1.1)	1/190 (0.5)
Pneumocephalus	2/181 (1.1)	1/190 (0.5)
Radius fracture	2/181 (1.1)	0/190 (0.0)
Skin injury	2/181 (1.1)	0/190 (0.0)
Vascular access site haematoma	2/181 (1.1)	0/190 (0.0)

n = number of subjects with data available by category; N = number of subjects in the analysis set.

Note: Denominator (N) of the percentage is based on the number of subjects in the analysis set.
Note: Adverse events that started on or after the date of unplanned embolic treatment in subjects who received unplanned embolic treatment during follow-up (beyond 10 days post randomization or surgery), were excluded from the randomization assignment in the summary table.

Table 8
Summary of Adverse Events (AEs) for MEMBRANE Clinical Study by Medical Dictionary for Regulatory Activities (MedDRA) Codes

	TRUFILL+SOC N=181	SOC Alone N=190
System Organ Class (SOC) Preferred Term (PT)	**Number of subjects n/N (%)**	**Number of subjects n/N (%)**
General disorders and administration site conditions		
Physical deconditioning	8/181 (4.4)	5/190 (2.6)
Pyrexia	6/181 (3.3)	4/190 (2.1)
Fatigue	4/181 (2.2)	1/190 (0.5)
Chest pain	3/181 (1.7)	4/190 (2.1)
Asthenia	2/181 (1.1)	2/190 (1.1)
Gait disturbance	2/181 (1.1)	2/190 (1.1)
Gastrointestinal disorders		
Vomiting	5/181 (2.8)	2/190 (1.1)
Constipation	4/181 (2.2)	6/190 (3.2)
Abdominal pain	3/181 (1.7)	3/190 (1.6)
Diarrhoea	3/181 (1.7)	1/190 (0.5)
Haematochezia	3/181 (1.7)	0/190 (0.0)
Dysphagia	2/181 (1.1)	0/190 (0.0)
Musculoskeletal and connective tissue disorders		
Arthralgia	5/181 (2.8)	8/190 (4.2)
Muscular weakness	4/181 (2.2)	2/190 (1.1)
Back pain	2/181 (1.1)	0/190 (0.0)
Musculoskeletal chest pain	2/181 (1.1)	1/190 (0.5)
Cardiac disorders		
Atrial fibrillation	4/181 (2.2)	0/190 (0.0)
Acute myocardial infarction	3/181 (1.7)	3/190 (1.6)
Tachycardia	3/181 (1.7)	0/190 (0.0)
Cardiac failure	2/181 (1.1)	3/190 (1.6)
Cardiac failure congestive	2/181 (1.1)	3/190 (1.6)
Metabolism and nutrition disorders		
Hypokalaemia	6/181 (3.3)	2/190 (1.1)
Hyponatraemia	3/181 (1.7)	3/190 (1.6)
Hypocalcaemia	2/181 (1.1)	0/190 (0.0)
Hypoglycaemia	2/181 (1.1)	2/190 (1.1)

n = number of subjects with data available by category; N = number of subjects in the analysis set.
Note: Denominator (N) of the percentage is based on the number of subjects in the analysis set.
Note: Adverse events that started on or after the date of unplanned embolic treatment in subjects who received unplanned embolic treatment during follow-up (beyond 10 days post randomization or surgery), were excluded from the randomization assignment in the summary table.

Table 8
Summary of Adverse Events (AEs) for MEMBRANE Clinical Study by Medical Dictionary for Regulatory Activities (MedDRA) Codes

	TRUFILL+SOC N=181	SOC Alone N=190
System Organ Class (SOC) Preferred Term (PT)	**Number of subjects n/N (%)**	**Number of subjects n/N (%)**
Psychiatric disorders		
Insomnia	5/181 (2.8)	5/190 (2.6)
Confusional state	3/181 (1.7)	2/190 (1.1)
Anxiety	2/181 (1.1)	0/190 (0.0)
Depression	2/181 (1.1)	1/190 (0.5)
Respiratory, thoracic and mediastinal disorders		
Cough	4/181 (2.2)	2/190 (1.1)
Oropharyngeal pain	3/181 (1.7)	0/190 (0.0)
Respiratory failure	3/181 (1.7)	4/190 (2.1)
Pulmonary embolism	2/181 (1.1)	1/190 (0.5)
Renal and urinary disorders		
Urinary retention	5/181 (2.8)	4/190 (2.1)
Acute kidney injury	3/181 (1.7)	4/190 (2.1)
Vascular disorders		
Hypertension	4/181 (2.2)	1/190 (0.5)
Hypotension	3/181 (1.7)	3/190 (1.6)
Deep vein thrombosis	2/181 (1.1)	1/190 (0.5)
Blood and lymphatic system disorders		
Anaemia	4/181 (2.2)	4/190 (2.1)
Thrombocytopenia	3/181 (1.7)	0/190 (0.0)
Skin and subcutaneous tissue disorders		
Rash	2/181 (1.1)	1/190 (0.5)
Ear and labyrinth disorders		
Vertigo	3/181 (1.7)	0/190 (0.0)
Cerumen impaction	2/181 (1.1)	0/190 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Lipoma	2/181 (1.1)	0/190 (0.0)
Reproductive system and breast disorders		
Benign prostatic hyperplasia	2/181 (1.1)	0/190 (0.0)

n = number of subjects with data available by category; N = number of subjects in the analysis set.
Note: Denominator (N) of the percentage is based on the number of subjects in the analysis set.
Note: Adverse events that started on or after the date of unplanned embolic treatment in subjects who received unplanned embolic treatment during follow-up (beyond 10 days post randomization or surgery), were excluded from the randomization assignment in the summary table.

Primary Effectiveness Results

The primary effectiveness endpoint was residual or re-accumulation of the SDH (>10 mm) at 6 months as assessed by an independent core laboratory or re-operation or surgical procedure on the SDH within 6 months post-randomization. In the test group, 106 surgical cohort subjects and 40 NSMM subjects contributed to the primary effectiveness endpoint. In the control group, 94 surgical cohort subjects and 37 NSMM subjects contributed to the primary effectiveness endpoint. Multiple imputation was used to impute missing data for subjects with missing primary endpoint data at 6 months (e.g., due to early withdrawal from the study, loss to follow up, or death). As shown in Table 9, the primary analysis resulted in an odds ratio of 0.475 (90% CI: 0.239, 0.944) for the surgical cohort favoring the TRUFILL n-BCA LES, and an odds ratio of 0.615 (90% CI: 0.266, 1.419) for the non-surgical cohort, where the upper confidence interval exceeded 1 which failed to meet significance. As shown in Table 10, the final combined estimate of the common odds ratio was 0.529 (90% CI: 0.308, 0.909) with a one-sided p-value of 0.044. Therefore, the primary effectiveness endpoint was met for the overall population.

Table 11 shows the reasons for primary effectiveness outcome events in the surgical cohort and the combined cohort (surgical + NSMM). Of note, 3/104 (2.9%) subjects in the test group and 7/86 (8.1%) subjects in the control group within the surgical cohort required re-operation or additional surgical procedures by 6 months which was the most common primary endpoint event in the control group. Additionally, 6/104 (5.8%) subjects in the test group and 3/86 (3.5%) subjects in the control group within the surgical cohort had primary effectiveness endpoint events due to residual or re-accumulation of the SDH (>10 mm). Of note, data presented in “event by reason” rows of Table 11 excludes patients that did not receive their treatment assignment, including several control patients that received a liquid embolic. These trends were similar in the combined cohort.

A sensitivity analysis was conducted using the PP and AT analysis sets. Importantly, the PP analysis set excluded 8 subjects in the test arm that did not receive the TRUFILL LES and 15 subjects in the control arm that did not receive their assigned treatment. The analysis on the PP analysis set resulted in a common OR of 0.776 (90% CI: 0.419, 1.437) for the combined cohort which did not meet significance for the primary endpoint and raises questions regarding the robustness of the estimate of the primary endpoint. However, analysis of the combined cohort on the AT analysis set, which analyzes subjects per the treatment received regardless of treatment assignment showed significance favoring the test group with a common OR of 0.426 (90% CI: 0.244, 0.743).

Table 9
Primary Effectiveness Endpoint by Cohort

Category	Surgical Cohort N=265	NSMM Cohort N=111
Primary effectiveness endpoint at 6 months		
Estimate of odds ratio with imputed data (90% CI)	0.475 (0.239, 0.944)	0.615 (0.266, 1.419)

Note: Odds ratio is defined as the ratio of the odds of event (failure) probability to event-free (success) probability in subjects with MMAE procedure vs. those without MMAE procedure. An OR <1 favors the treatment with MMAE of less likelihood of primary effectiveness endpoint event.

Table 10
Primary Effectiveness Endpoint

Category	TRUFILL+SOC N=188	SOC Alone N=188	Overall N=376
Primary effectiveness endpoint at 6 months with observed data, n/N (%)	17/146	29/131	
Combined estimate for common odds ratio with imputed data			0.529
90% CI (Mantel Haenszel method)			(0.308,0.909)
p-value of one-sided Cochran-Mantel-Haenszel (CMH) test			0.044

Note: Common odds ratio is defined as the ratio of the odds of event (failure) probability to event-free (success) probability in subjects with MMAE procedure vs. those without MMAE procedure. An OR <1 favors the treatment with MMAE of less likelihood of primary effectiveness endpoint event.

Table 11
Primary Effectiveness Endpoint by Reason

Category	Surgical Cohort		Combined Cohort	
	TRUFILL + Surgery	Surgery Alone	TRUFILL + SOC	SOC Alone
Primary effectiveness endpoint at 6 months, n/N* (%)	9/106 (8.5)	19/94 (20.2)	17/146 (11.6)	29/131 (22.1)
Missing data, n	27	38	42	57
Event by reason+, n/N* (%)				
Due to residual or re-accumulation of the SDH (>10mm) per independent core lab at 6 months	6/104 (5.8)	3/86 (3.5)	10/143 (7.0)	6/119 (5.0)
Due to re-operation or surgical procedure on the SDH within 6 months	3/104 (2.9)	7/86 (8.1)	6/143 (4.2)	10/119 (8.4)
Due to embolic treatment (Trufill n-BCA or non-Trufill n-BCA) other than index procedure prior to 6-month	0/104 (0.0)	0/86 (0.0)	0/143 (0.0)	0/119 (0.0)

Category	Surgical Cohort		Combined Cohort	
	TRUFILL + Surgery	Surgery Alone	TRUFILL + SOC	SOC Alone
Due to death related to study device (Trufill n-BCA) or due to underlying disease status within 6 months per CEC	0/104 (0.0)	2/86 (2.3)	0/143 (0.0)	2/119 (1.7)

CEC = clinical events committee; SDH = chronic subdural hematoma; n = number of subjects by endpoint; N =number of subjects in the analysis set; SOC = standard of care surgery or NSMM.
Note: Primary effectiveness endpoint event is defined as residual or re-accumulation of the SDH (>10 mm) at 6 months per independent core laboratory or re-operation or surgical procedure on the SDH within 6 months post randomization.
Note: A subject may be considered as the primary effectiveness endpoint with one or more events; however, a subject is counted once in each category.
Note: Denominator (N*) for the percentage is based on the number of subjects with non-missing values of the primary effectiveness endpoint.
[+] Denominator is based on the number of subjects that received their assigned treatment without any crossover

Subgroup analyses

The following baseline characteristics were evaluated for potential association with the primary effectiveness outcome: ethnicity, race, age, sex and region and site homogeneity. Significant differences among subgroups were not identified. Subgroup analyses were exploratory in nature and should be interpreted with caution, as the study was not specifically powered for subgroup comparisons.

Primary Safety Endpoint

The primary safety endpoint was overall incidence of AEs through 6 months and was based on the AT analysis set of 371 patients available through the 6-month evaluation. Within the AT analysis set, 414 AEs occurred in 130/181 (71.8%) subjects in the test arm and 392 AEs occurred in 124/190 (65.3%) subjects in the control arm. Table 12 presents the overall incidence of adverse events by seriousness, severity, and relation through 6 months within the ITT analysis set, excluding subjects who did not receive their treatment assignment. Of the 180 subjects in the test arm that received TRUFILL LES, 12/180 (6.7%) subjects experienced AEs related to the device and 1/180 (0.6%) subject experienced an SAE (cerebral artery infarct) related to the device. The most common device related AE was seizure which occurred in 11/180 (6.1%) subjects. In addition, 4/180 (2.2%) subjects experienced SAEs related to the embolization procedure. A total of 2/180 (1.1%) patients experienced unintended vessel occlusion, and 4/180 (2.2%) subjects experienced vascular access site complications. Catheter entrapment was not observed in any subjects receiving TRUFILL LES. Table 13 presents neurological deaths and neurological events of interest through 6 months within the ITT analysis set, excluding subjects that did not receive their treatment assignment. No neurologic deaths associated with the device or embolization procedure were observed. Overall, the use of the TRUFILL LES did not present any unknown risks that have not been previously described.

Table 12
Overall Incidence of Adverse Events by Seriousness, Severity, and Relation through 6 months

Category	TRUFILL+SOC N=188 Number of subjects n/N* (%)	SOC Alone N=188 Number of subjects n/N* (%)
All AEs (including SAEs, non-SAEs)	129/180 (71.7)	110/173 (63.6)
Non-SAEs	110/180 (61.1)	95/173 (54.9)
Serious adverse events (SAEs)	50/180 (27.8)	49/173 (28.3)
SAEs Related to Embolization Procedure through 6 months	4/180 (2.2)	Not Applicable
SAEs Related to TRUFILL through 6 months	1/180 (0.6)	Not Applicable
AEs Related to TRUFILL through 6 months	12/180 (6.7)	Not Applicable
Severe AEs through 6 months	24/180 (13.3)	32/173 (18.5)
Unintended Vessel Occlusion	2/180 (1.1)	Not Applicable
Catheter Entrapment	0/180 (0.0)	Not Applicable
Access Site Complications	4/180 (2.2)	Not Applicable
TRUFILL LES Migration	0/180 (0.0)	Not Applicable

n = number of subjects with data available by category; N = number of subjects in the analysis set.
Note: Denominator (N) of the percentage is based on the number of subjects that received their assigned treatment without any crossover.*

Table 13
Neurologic Death and Neurologic Events of Interest through 6 Months

Category	TRUFILL+SOC N=188 Number of subjects n/N* (%) [Number of events]	SOC Alone N=188 Number of subjects n/N* (%) [Number of events]
All Neurologic Deaths[1]	3/180 (1.7) [3]	4/173 (2.3) [4]
Related to Study Device[1]	0/180 (0.0) [0]	0/173 (0.0) [0]
Related to Embolization Procedure[1]	0/180 (0.0) [0]	0/173 (0.0) [0]
Related to Surgery Procedure[1,2]	0/129 (0.0) [0]	4/123 (3.0) [4]
Related to SDH Medication[1]	0/180 (0.0) [0]	0/173 (0.0) [0]
Other[3]	3/180 (1.7) [3]	0/173 (0.0) [0]

Stroke[1]	3/180 (1.7) [3]	2/173 (1.2) [2]
Cerebral Infarction	2/180 (1.1) [2]	2/173 (1.2) [2]
Serious Intracranial Hemorrhage	2/180 (1.1) [2]	7/173 (4.0) [7]
New onset of seizures[1]	11/180 (6.1) [11]	6/173 (3.5) [6]
TIA	1/180 (0.6) [1]	0/173 (0.0) [0]
Ipsilateral Visual Symptoms	2/180 (1.1) [2]	1/173 (0.6) [1]

n = number of subjects with data available by category; N = number of subjects in the analysis set.
Note: Denominator (N) of the percentage is based on the number of subjects that received their assigned treatment without any crossover.*
[1]Neurological deaths and relatedness, stroke, and new onset of seizures were adjudicated by the Clinical Events Committee (CEC), and all other events were site reported.
[2]Denominator is based on the number of patients receiving surgery.
[3]Other relatedness is defined as relatedness not pertaining to study device, embolization procedure, surgery procedure, or SDH medication.

Secondary Effectiveness Endpoint

Good Functional Outcome at 3 Months (mRS 0-2 or No Worsening from Baseline if Baseline mRS ≥3)

An assessment of good functional outcome at 3 months (mRS 0-2 or no worsening from baseline if baseline mRS ≥3) was performed in the ITT analysis set. As shown in Table 14 122/143 (85.3%) of test group subjects and 104/135 (77.0%) of control group subjects had good functional outcomes at 3 months demonstrating non-inferiority of the test group to the control group with regard to good functional outcome.

Table 14
Good Functional Outcome at 3 months – MMAE Treatment vs. SOC Treatment

Category	TRUFILL+SOC N=188	SOC Alone N=188
Good functional outcome (mRS 0-2 or no worsening from baseline if baseline mRS ≥ 3) at 3 months with observed data, n/N* (%)	122/143 (85.3)	104/135 (77.0)
Combined estimate for risk difference with imputed data		0.073
90% CI		(0.001, 0147)

n = number of subjects by endpoint; N = number of subjects in the analysis set.
Note: Risk difference is calculated as the difference of the event rates of the treatment arm with TRUFILL vs. standard of care arm without TRUFILL.
Note: Denominator (N) of the percentage of the observed data is calculated based on the non-missing value of the endpoint by category.*

Additional analyses:

A post-hoc analysis was completed using a composite endpoint with the following components evaluated at 6 months post-randomization:

(1) Residual or re-accumulation of the SDH compared to baseline hematoma,
(2) AEs of symptomatic subdural hematoma within 6-months,
(3) All-cause mortality within 6-months,

(4) Worsening of the Markwalder Grading Scale (MGS) at 6 months compared to baseline MGS.

The outcomes of this post-hoc analysis are shown in Table 15 for the composite endpoint and each component of the composite endpoint. Within the surgical cohort, each component of the post-hoc endpoint trended favorably for the test group with the exception of worsening in MGS at 6 months compared to baseline.

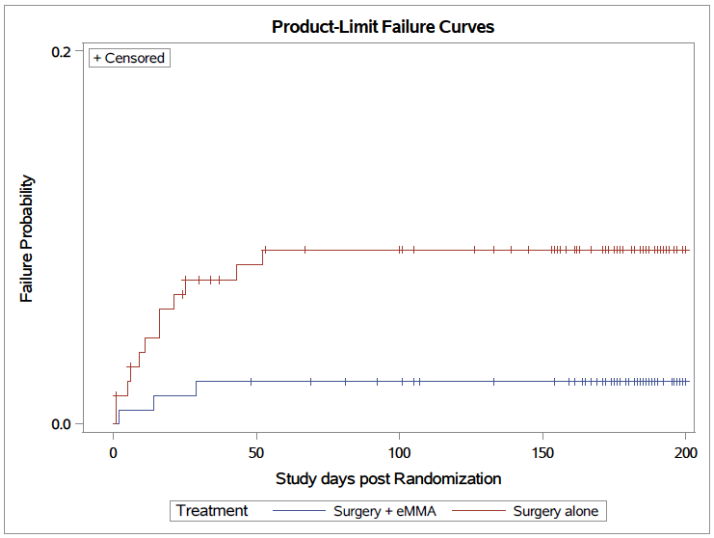
Table 15

Category	Surgical Cohort		Combined Cohort	
	TRUFILL + Surgery	Surgery Alone	TRUFILL + SOC	SOC Alone
Post hoc effectiveness endpoint at 6 months, n/N* (%)	13/106 (12.3)	26/93 (28.0)	22/146 (15.1)	37/134 (27.6)
Missing data, n	27	39	42	54
Event by reason⁺, n/N* (%)				
Due to worsening in hematoma volume at 6 months compared to baseline	4/104 (3.8)	6/85 (7.1)	7/143 (4.9)	8/122 (6.6)
Due to symptomatic SDH as an AE through 6 months	5/104 (4.8)	10/85 (11.8)	9/143 (6.3)	12/122 (9.8)
Due to all-cause mortality through 6 months	1/104 (1.0)	11/85 (12.9)	6/143 (4.2)	16/122 (13.1)
Due to worsening MGS at 6 months compared to baseline	5/104 (4.8)	1/85 (1.2)	7/143 (4.9)	1/122 (0.1)

CEC = clinical events committee; SDH = chronic subdural hematoma; n = number of subjects by endpoint; N = number of subjects in the analysis set.
Note: Primary effectiveness endpoint event is defined as residual or re-accumulation of the SDH (>10 mm) at 6 months per independent core laboratory or re-operation or surgical procedure on the SDH within 6 months post randomization.
Note: A subject may be considered as the primary effectiveness endpoint with one or more events; however, a subject is counted once in each category.
Note: Denominator (N) for the percentage is based on the number of subjects with non-missing values of the primary effectiveness endpoint.*
⁺Denominator is based on the number of subjects that received their assigned treatment without any crossover.

A Kaplan-Meier analysis of time to surgical procedure on SDH post-randomization was performed. As shown in Figure 2, all post-randomization surgical procedures occurred within 44 days of randomization.

Figure 2
Kaplan-Meier Analysis of Time to Surgical Procedure on SDH post Randomization



Clinical study conclusions

The results of the MEMBRANE study demonstrated that adjunctive use of TRUFILL n-BCA Liquid Embolic System (TRUFILL n-BCA + surgery) is superior in effectiveness compared to surgery alone for embolization in the Middle Meningeal Artery (MMA) for the treatment of SDH in preventing hematoma recurrence/progression requiring surgical drainage. Furthermore, subjects treated with TRUFILL n-BCA Liquid Embolic System as an adjunct to surgery exhibited good functional outcomes, as measured by mRS at three months post-embolization. TRUFILL n-BCA Liquid Embolic System was also demonstrated to be safe for treating SDH, with a safety profile comparable to that of surgery alone. Overall, the findings of the MEMBRANE study indicate that the benefits of TRUFILL n-BCA outweigh the potential risks for the proposed intended use of embolization of the Middle Meningeal Artery (MMA) for the treatment of symptomatic subacute or chronic SDH as an adjunct to surgery.

Warranty

Cerenovus warrants that this medical device is free from defects in both materials and workmanship. Any other express or implied warranties, including warranties of merchantability or fitness, are hereby disclaimed. Suitability for use of this medical device for any particular surgical procedure should be determined by the user in conformance with the manufacturer's instructions for use. There are no warranties that extend beyond the description on the face hereof.

Symbols

Do not resterilize


Do not use if package is damaged

 Manufacturer

 Made in

 Nonpyrogenic

 Quantity

 Do not reuse

 Radiopaque

 Do not autoclave

 Consult instructions for use

 Caution

 MR Conditional

 Keep dry

 Keep away from sunlight

Electronic IFU website

TRUFILL™ n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System Procedural Set

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Suites 215 & 315
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LCN 208932-001-001/B

Revised 2025/12
www.e-ifu.com

IMPORTANT INFORMATION
Please Read Before Use

TRUFILL™ n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System Procedural Set

n-Butyl Cyanoacrylate	STERILE	Sterilized using dry heat, and
	STERILE EO	Sterilized using ethylene oxide gas
Tantalum Powder	STERILE R	Sterilized using irradiation.
Ethiodized Oil	STERILE	Sterilized using moist heat
Procedural Set	STERILE EO	Sterilized using ethylene oxide gas.

℞ Only

Description
The TRUFILL n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System Procedural Set is an artificial embolization device, comprised of TRUFILL n-Butyl Cyanoacrylate (n-BCA), TRUFILL Ethiodized Oil and TRUFILL Tantalum Powder. These components must be used as a system. They are not intended for use as individual components. Also included in the set are the accessories necessary to initiate the procedure.

The TRUFILL n-BCA Liquid Embolic System is used under fluoroscopic guidance to obstruct or reduce blood flow to embolize arteriovenous malformations (AVMs) and the Middle Meningeal Artery (MMA). Upon contact with body fluids or tissue, the mixture polymerizes into a solid material. The n-BCA is a clear, free-flowing liquid that polymerizes via an anionic mechanism. Ethiodized oil is a straw-to-amber colored, oily fluid containing iodinated poppy seed oil and is used as a radiopaque polymerizing retardant. The amount of Ethiodized Oil used will vary the rate of polymerization. Tantalum (Ta) powder is a finely ground, irregularly shaped, dark gray metal that can be used with Ethiodized Oil to make the n-BCA radiopaque.

The TRUFILL n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System Procedural Set is available in two kit configurations:

Product Code	Description
632400NA	(2) 1 g tubes of n-BCA, (2) self-piercing caps, 1 g tube of Ta Powder, 10 mL vial of Ethiodized Oil, (3) 1 mL and (3) 3 mL

	syringes, 30 mL beaker, 18 G blunt fill needle, (2) 21 G Hypodermic needles, syringe labels
632500NA	1 g tube of n-BCA, self-piercing luer cap, 1 g tube of Ta Powder, 10 mL vial of Ethiodized Oil, (3) 1 mL and (3) 3 mL syringes, 30 mL beaker, 18 G blunt fill needle, (2) 21 G Hypodermic needles, syringe labels

Indications

The TRUFILL n-BCA Liquid Embolic System is indicated for the embolization of cerebral arteriovenous malformations (AVMs) when pre-surgical devascularization is desired and for embolization of the Middle Meningeal Artery (MMA) for the treatment of symptomatic subacute and chronic Subdural Hematoma (SDH) as an adjunct to surgery.

Contraindications
Separate use of the individual components of the TRUFILL n-BCA Liquid Embolic System Procedural Set is contraindicated. The components must be used as a system.

Ethiodized oil alone should not be injected:
- Intravascularly
- Intrathecally
- Intrabronchially

Use of the TRUFILL n-BCA Liquid Embolic System is contraindicated when any of the following conditions exist:
- Optimal catheter placement is not possible.
- A previous history of reactions to cyanoacrylates exists.
- A previous history of hypersensitivity to Ethiodized Oil exists.
- A previous history of reactions to iodine exists.
- Provocative testing indicates intolerance to the occlusion procedure.
- Vasospasm stops blood flow.
- High blood flow precludes safe infusion of an embolic agent.

WARNINGS
- The TRUFILL n-BCA Liquid Embolic System should only be used by physicians trained in interventional endovascular procedures at medical facilities with the proper imaging equipment
- Prior to injection it is essential to determine, via fluoroscopy, the radiopacity of the mixture by comparison with a similar syringe containing contrast. Inadequate visualization of the mixture could cause inappropriate embolization.
- The n-BCA is a fast-setting adhesive capable of adhering to most body tissues. It will polymerize in the presence of anionic media, such as body fluids or tissues. Proper handling is required to avoid premature polymerization and occlusion of the delivery system or adherence of the catheter tip to the vessel wall.

- TRUFILL Ethiodized Oil should never be used as a radiopaque contrast agent to assess hemodynamics and should be used only to prepare the TRUFILL n-BCA Liquid Embolic System.
- Do not dilute or mix TRUFILL n-BCA with any substance other than the ethiodized oil or tantalum powder included in the TRUFILL kit.
- Embolization could influence blood flow patterns, thereby subjecting arteries supplying the embolization target to increased pressures. Increased arterial pressures can result in hemorrhagic complications.
- Laboratory studies have determined that TRUFILL Ethiodized Oil can elute over time.
- Life threatening and fatal reactions can occur without warning. A fully equipped emergency cart and resuscitation equipment must be readily available at all times, along with personnel competent in recognizing and treating reactions of all severity.

Precautions

- Store in a cool, dark, dry place.
- Inspect the sterile package carefully. Do not use if:
    - the package or seal appears damaged,
    - the contents appear damaged,
    - the expiry date has passed.

- The safety and performance of the TRUFILL n-BCA Liquid Embolic System has not been demonstrated in pediatric populations.
- Angiography is necessary for pre-embolization evaluation, operative control, and post-embolization follow-up.
- Verify that the n-BCA is a clear and free-flowing liquid prior to use. Do not use the product if material has thickened, discolored, or contains particulate matter. Discard and open a new TRUFILL n-BCA Liquid Embolic System.
- Use of a 21 G needle to aspirate the n-BCA into an appropriate injection syringe is recommended.
- The n-BCA will adhere to most surfaces. Avoid contact with non-disposable surfaces or surfaces that cannot be cleaned with acetone.
- Gloves and eye/face protection are recommended when handling n-BCA.
- Verify that the catheters and accessories used in direct contact with the system are clean and compatible with the material and do not trigger polymerization or degrade upon contact. All accessories contained in this procedural set comply with these requirements.
- Do not use with any device containing polycarbonate. Cyanoacrylates cause polymers containing polycarbonate to deteriorate.
- Avoid contact with the eyes. In case of accidental contact, immediately wash with water and seek medical attention.
- Therapeutic embolization should not be performed when high blood flow precludes the safe infusion of embolic agents.
- Do not use saline or any ionic fluid when handling or mixing n-BCA to avoid premature polymerization.

Training

TRUFILL n-BCA Liquid Embolic System Procedural Set should only be used by physicians trained in interventional endovascular procedures at medical facilities with the proper imaging equipment.

Potential Adverse Events

Potential adverse events associated with embolization procedures can occur at any time during or after the procedure. These include, but are not limited to:

- Access site injury (including bleeding, bruising, infection, pain)
- Allergic reaction/anaphylactic shock
- Catheter glued inside vessel (catheter entrapment)
- Cerebral infarction
- Death
- Early polymerization
- Embolism, including pulmonary and thromboembolism
- Headache
- Hematoma
- Hemorrhage
- Infection/inflammation
- Late polymerization
- Myocardial infarction
- Nausea/vomiting
- Neurological deficits
- Non-target embolization (passage of embolic material into normal vessels adjacent to the target) which may cause but not limited to blindness, dysesthesias of the face (increased or decreased sensitivity), facial weakness, or deafness
- Occluded catheter
- Renal failure
- Seizure
- Stroke
- Subdural hematoma recurrence
- Vasospasm
- Vessel dissection, perforation, and injury

Use of device requires fluoroscopy which presents potential risks to physicians and patients associated with x-ray exposure. Possible risks include, but are not limited to, the following:

- Alopecia
- Burns ranging in severity from skin reddening to ulcers
- Cataracts
- Delayed neoplasia

How Supplied

This product is for SINGLE USE ONLY; DO NOT RESTERILIZE. Cerenovus will not be responsible for product that is resterilized, nor accept for credit or exchange product that has been opened but not used.

As long as the inner unit is not opened or damaged, the Trufill n-BCA Liquid Embolic System Procedural Set is sterile and nonpyrogenic.

The syringe labels are sterile.

Storage and Handling
Remove the components from the carton just prior to use. Protect the Ethiodized Oil from light.

Magnetic Resonance Imaging (MRI) Safety Information

MR Conditional 

MRI Safety Information

A person with the TRUFILL n-BCA Liquid Embolic System and Procedural Set may be safely scanned under the following conditions. Failure to follow these conditions may result in injury.

Device Name	TRUFILL n-BCA Liquid Embolic System and Procedural Set
Static Magnetic Field Strength (Bo)	1.5 T or 3.0 T
Maximum Spatial Field Gradient	40 T/m (4,000 gauss/cm)
RF Excitation	Circularly Polarized (CP)
RF Transmit Coil Type	There are no Transmit Coil restrictions
RF Receive Coil Type	Any
Operating Mode	Normal Operating Mode
Maximum Whole-Body SAR	2 W/kg (Normal Operating Mode)
Maximum Head SAR	3.2 W/kg (Normal Operating Mode)
Scan Duration	2 W/kg whole-body averaged SAR for 60 minutes of continuous RF (a sequence or back to back series/scan without breaks)
MR Image Artifact	The presence of this implant may produce an image artifact of up to 8 mm.

Directions for Use

CAUTION: **Do not use with syringes containing polycarbonate. Verify syringe material before use.**

- The TRUFILL n-BCA Liquid Embolic System Procedural Set is designed and tested to be delivered under fluoroscopy through the PROWLER™ and TRANSIT™families of microcatheters. Use with any other catheter has not been evaluated

- The n-BCA, Ethiodized Oil, and Tantalum Powder (if used) mixture should be prepared using the provided 1mL or 3 mL syringe (made of polyethylene or polypropylene).
- Use the provided 1 mL to 3 mL syringe with Luer lock made of polyethylene or to inject the mixture through the microcatheter.
- Remove the Ethiodized Oil from the glass ampule using a blunt fill needle.
- Only the provided luer cap or 21 G needle should be used to pierce the n-BCA tube.
- Use the provided 30 mL glass beaker for preparation of the mixture.

Pre-Embolization

TRUFILL n-BCA Liquid Embolic System Procedural Set should only be used by physicians trained in interventional endovascular procedures at medical facilities with the proper imaging equipment.

Serious, including fatal, consequences can result with the use of the TRUFILL n-BCA Liquid Embolic System Procedural Set without adequate training. Contact your Johnson and Johnson Medtech Neurovascular sales representative for information on training courses.

Prior to use, perform baseline angiography to determine the vascular supply to the lesion. **Note:** For treatment of AVMs, the angiogram should demonstrate the route of the catheter entry as well as identify relevant collateral circulation.
1. Introduce the infusion catheter according to standard technique. Position the infusion catheter as close as possible to the treatment site to avoid inadvertent occlusion of normal vessels.
2. Perform contrast injections to assess hemodynamics prior to embolization. **CAUTION: The Ethiodized Oil must not be used as a radiopaque contrast agent to assess hemodynamics and must be used only to prepare the n-BCA mixture. Ethiodized Oil is contraindicated for intravascular, intrathecal or intrabronchial use.**

Recommended Mixtures
1. Radiopacity of the n-BCA mixture is accomplished by adding Ethiodized Oil and Tantalum Powder to the n-BCA. These additives will also extend the polymerization time of the n-BCA.
2. Recommended ratios of n-BCA to Ethiodized Oil and **T**antalum **P**owder vary depending on the location of injection and flow rates.
CAUTION: **Therapeutic embolization should not be performed when high blood flow precludes the safe infusion of embolic agent.** Higher concentrations of Ethiodized Oil increase the polymerization time, which allows for more distal penetration. Higher concentrations of n-BCA result in a faster polymerization rate, which will allow the physician to embolize the vasculature more proximally. Ratios used in the prospective, randomized clinical study of the **TRUFILL n-BCA Liquid Embolic** System varied from 10% to 70% n-BCA and 30% to 80% Ethiodized Oil by volume. Refer to Figure 1 for polymerization rates at various ratios. Ratios outside these parameters have not been tested clinically and are not recommended. Guidelines are recommended in Table 4.

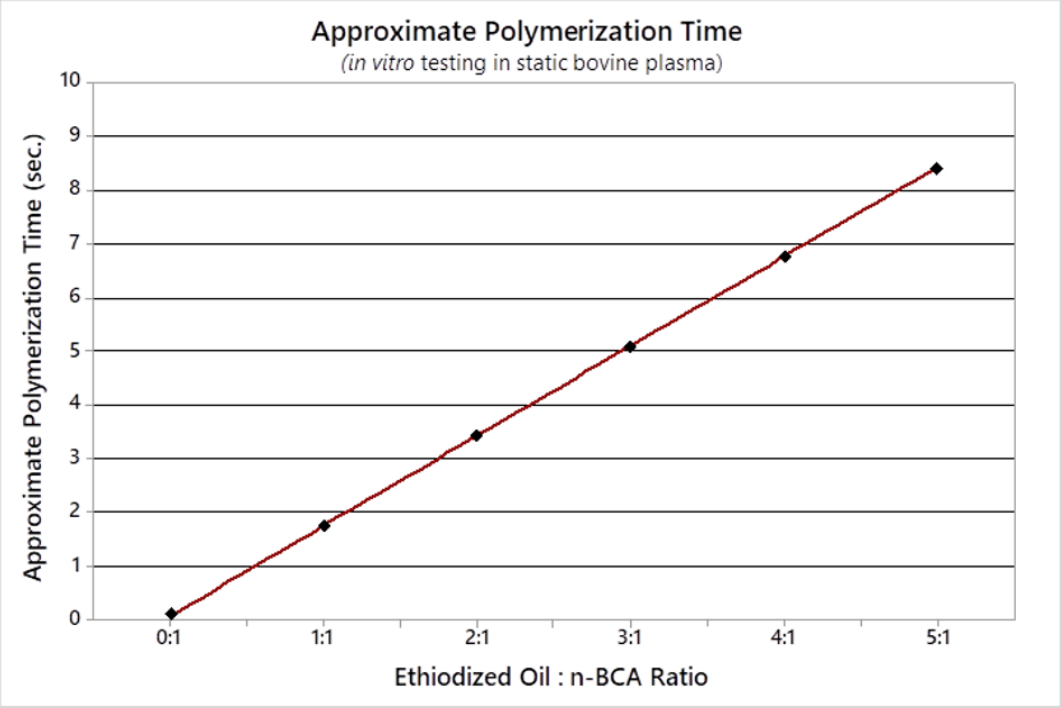


Figure 1

Setup

1. Snap the top off the neck of the Ethiodized Oil vial using a sterile alcohol wipe.
2. Pour 5% dextrose solution in water into the tray cavity.

Preparation of Mixture

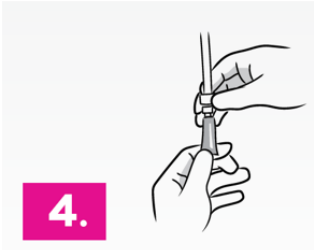
1. Using a blunt fill needle, withdraw the required amount of Ethiodized Oil from the vial**.** Deposit the oil into a clean, sterile glass beaker.
2. If using, add tantalum to the oil in the beaker

3.Stir until the mixture appears homogenous.

CAUTION: Thoroughly mix the radiopacifying agents prior to adding the n-BCA. Do not use Tantalum Powder alone with n-BCA.

4. To remove the TRUFILL n-BCA from the tube, attach the self-piercing cap to a Luer lock syringe and then attach the other end of the cap (with the syringe connected to it) to the n-BCA tube. While screwing the cap onto the tube you will first feel resistance which will ease when the seal of the tube is punctured. Continue twisting the cap onto the tube

until resistance builds again, signaling a proper seal between the syringe, cap, and tube. Avoid spilling the n-BCA, by keeping the tube crimped side down and the cap with syringe up until a proper seal is achieved. To withdraw the n-BCA, turn the syringe-cap-tube assembly to the tube crimped side up and extract the desired amount of n-BCA into the syringe. Inspect the n-BCA to verify that it is clear and free flowing. Do not use any material that has thickened, discolored, or contains particulate matter. Discard and open a new TRUFILL n-BCA Liquid Embolic System



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5. Add the desired amount of n-BCA to the sterile glass beaker.

6. Mix thoroughly until the mixture appears homogenous.

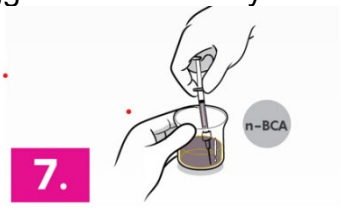
WARNING: Polymerization time, viscosity, and injection technique are interrelated and affect the progress of embolization. The appropriate formulation of any additives is dependent upon the expert evaluation of the relationship of anatomy, hemodynamics, and the catheter system. Figure 1 illustrates the polymerization rates obtained during in vitro testing in static bovine plasma.

WARNING: A 0:1 Ethiodized Oil to n-BCA ratio should never be used. Refer to the *"Recommended Mixtures*" section and Figure 1 for recommended ratios.

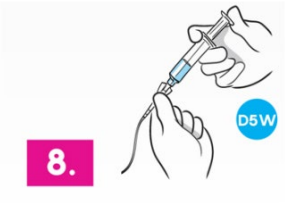
To determine whether your mixture is sufficiently radiopaque for visualization, compare it under fluoroscopy to a similar syringe full of contrast media.

Injection of Mixture

7. Aspirate the mixture into an appropriate injection syringe and verify that no material is agglomerated. Verify that the mixture is well suspended and free of air bubbles.



8. Prepare the microcatheter by thoroughly rinsing the outside of the catheter hub and flushing the catheter with a 5% dextrose solution in water.



Note: Do not rinse the glass beaker and/or the syringes with 5% dextrose prior to use. Prolonged contact of n-BCA with 5% dextrose could initiate the polymerization process.

9. Positioning the syringe tip slightly upwards (this will minimize the potential for agglomerated tantalum to obstruct the catheter lumen), inject the mixture through the microcatheter, using hand control and high-resolution fluoroscopic monitoring.
WARNING: If resistance is met during injection, do not attempt to clear or overcome the resistance by applying increased pressure. If this occurs, determine the cause of resistance and remove the catheter, if necessary. Applying increased pressure could result in rupture of the catheter and deposition of the mixture in an undesired area.

10. After injection is completed, immediately aspirate with the injection syringe and rapidly withdraw the catheter to prevent adherence of the catheter tip and to ensure that no unpolymerized mixture will leak during catheter withdrawal.

Note: **If the microcatheter tip becomes glued to the vascular site, it may be necessary to seek surgical intervention.**

11. Following each injection, discard the microcatheter and syringe.

12. Discard any opened and unused n-BCA, Ethiodized Oil, and tantalum powder.

Information to be supplied to the patient
After surgery, surgeons are to provide the patient with the Patient ID Card with information on the implant(s) used. Patients should be advised to carry the patient implant card to facilitate medical care in case of emergency.

Patient Information

Your doctor has implanted the Cerenovus TRUFILL n-BCA Liquid Embolic System**.**

Device Description

The TRUFILL n-BCA Liquid Embolic System is an artificial device used by doctors to block or decrease blood flow to treat abnormal blood vessels in the head.

Device Materials
TRUFILL n-BCA liquid embolic system is made up of three parts:

1. **n-BCA:** A glue that hardens to reduce blood flow. Contains:
n-Butyl Cyanoacrylate (nBCA) 99.0%n-Butyl Cyanoacetate; Sulfur Dioxide; Butylated Hydroxyanisole

It is mixed with:

2. **Ethiodized Oil:** Used to control the n-BCA hardening rate. Contains: Ethyl esters of iodized fatty acids of poppy seed oil.

It can also be mixed with:

3.Tantalum Powder: A finely ground, dark gray metal. This allows the device to be seen on X-ray. Contains**:**
Tantalum

Tell your doctor before surgery about any allergies you have to cyanoacrylates, ethiodized oil or iodine.

Information for Safe Use
Make sure to follow your doctors' orders for general safety.
Magnetic Resonance Imaging (MRI) is a test used to diagnose certain diseases.
Also, it can be used during medical procedures.
Before having an MRI, tell your doctors if you have an implanted medical device. **You can provide this document to your doctors so that they have the necessary information for performing a safe MRI.**

MRI Safety Information

A person with the TRUFILL n-BCA Liquid Embolic System and Procedural Set may be safely scanned under the following conditions. Failure to follow these conditions may result in injury.

Device Name	TRUFILL n-BCA Liquid Embolic System and Procedural Set
Static Magnetic Field Strength (Bo)	1.5 T or 3.0 T
Maximum Spatial Field Gradient	40 T/m (4,000 gauss/cm)
RF Excitation	Circularly Polarized (CP)
RF Transmit Coil Type	There are no Transmit Coil restrictions
RF Receive Coil Type	Any
Operating Mode	Normal Operating Mode

Maximum Whole-Body SAR	2 W/kg (Normal Operating Mode)
Maximum Head SAR	3.2 W/kg (Normal Operating Mode)
Scan Duration	2 W/kg whole-body averaged SAR for 60 minutes of continuous RF (a sequence or back to back series/scan without breaks)
MR Image Artifact	The presence of this implant may produce an image artifact of up to 8 mm.

Patient Information Portal

Any updated information will be provided on our website, ic.jnjmedicaldevices.com.

Information specific to your implant, including the serial number, unique device identifier, etc. are included on the implant card as well as in patient records kept by your healthcare provider.

Clinical Trials

TRUFILL n-BCA Clinical Trial for Treatment of Cerebral AVMs

Study Design

A prospective, multi-center, single-blind, randomized study was conducted to determine whether the TRUFILL n-BCA Liquid Embolic System was as safe and effective as poly-vinyl alcohol (PVA) for use in the obliteration of cerebral AVMs when pre-surgical devascularization is desired. The primary effectiveness outcome was the degree of vascular occlusion (percent nidus/lesion reduction and number of vessels occluded) as determined by the angiographic core laboratory. Secondary effectiveness outcomes were the length of time to resect the AVM and the number of transfusions required/total blood loss during the surgery. Primary safety outcomes for comparison to control treatment were the incidences of device-related complications, procedural complications, intracranial events, and unanticipated adverse device effects. Other safety measures, clinical neurological examinations, Glasgow Outcome Scores, and NIH Stroke Scale scores, were summarized at each of the follow-up time periods: post procedure, pre surgery, and post-surgery. Patients enrolled in the study were those who had an AVM that required preoperative devascularization as determined angiographically. Patients with Spetzler-Martin grade III, IV and V AVMs were treated. Patients with grade I and II lesions were treated if the anticipated benefit of the embolization was greater than the risk of the embolization procedure, and if the AVM feeding pedicle was located in an area that was difficult to surgically access. Conjunctive therapy using coils was permitted prior to embolization to slow the flow rate (if needed) or if a portion of the AVM contained blood vessels that were larger than the largest size of PVA available. Patients who had been previously embolized with PVA or

cyanoacrylate and patients with a known sensitivity to iodine containing contrast reagents were excluded from the study.

Patient Accounting

A total of 104 patients were enrolled into the study, 52 patients were randomized into each treatment group. Three patients of the PVA group were determined not able to be evaluated for the effectiveness analysis. Two crossover patients were randomized to PVA but were treated with n-BCA and one PVA patient was not used for effectiveness analyses due to inadequate source documentation. Four n-BCA patients were not embolized and therefore not included in the effectiveness analyses. Two patients were not embolized due to an inability to subselect the feeder vessel. One patient was not embolized because the physician deemed the location and type of AVM too dangerous to embolize. Finally, one patient was embolized with coils at Stage 1 and was to receive n-BCA during Stage 2 but withdrew consent. Therefore, the total number of patients who were included in the primary effectiveness outcome analysis was 97; 48 patients in the n-BCA group and 49 patients in the PVA group. The safety data set included 54 n-BCA and 52 PVA patients. Two patients who were randomized to PVA, but who received n-BCA after failed attempts to effectively embolize with PVA, have their complications listed (n-BCA or PVA) by when they occurred, i.e., during embolization or during surgical resection. Four of the five complications these patients experienced occurred during the PVA embolization stage and therefore are listed as PVA complications. One complication (other – considerable bleeding) occurred during resection after n-BCA embolization and, therefore, is listed as an n-BCA complication.

Methods

Preembolization and postembolization angiograms were obtained to determine the extent of occlusion achieved. The angiograms were sent to the angiographic core laboratory where anterior/posterior (AP) and lateral views of the nidus and selective arteriograms of the selected feeding pedicles were evaluated.

Adverse Events

A total of 104 patients (52 **TRUFILL** n-BCA Liquid Embolic System, 52 poly-vinyl alcohol (PVA) (control)) were enrolled for safety evaluation in a clinical trial for the treatment of cerebral AVMs. Two patients who were randomized to PVA, but who received n-BCA after failed attempts to effectively embolize with PVA, have their complications listed (n-BCA or PVA) by when they occurred, i.e., during embolization or during surgical resection. Four of the five complications these patients experienced occurred during the PVA embolization stage and therefore are listed as PVA complications. One complication (other – considerable bleeding) occurred during resection after n-BCA embolization and, therefore, is listed as an n-BCA complication. Therefore, the number of patients used for calculation of the incidence of adverse events in the n-BCA group is 54. Fifty-two percent of the patients in the n-BCA group and 54% of the patients in the PVA group (n-BCA: 51.9%, N = 28, and PVA: 53.9%, N = 28) had at least one complication. There was one unanticipated adverse device event (UADE) reported for a patient in the n-BCA group during the study, described in Table 1.

Two patients died during the treatment period; one due to cerebellar hemorrhage (n-BCA) and the other due to intracerebral hemorrhage (PVA), and 2 patients (PVA) died post-resection. The treatment period was defined as from pre-surgical embolization up through surgical resection. All reported adverse events that occurred in the n-BCA System cohort in the pivotal clinical study are listed in Table 1. The adverse events are listed in descending order according to frequency as observed for the study treatment group.

Adverse events associated with embolization procedures (including those observed during the clinical study), can occur at any time during or after the procedure. These adverse events include (in alphabetical order): allergic reaction, AVM rupture, catheter glued inside vessel, death, early polymerization, headache, hemorrhage, infection/inflammation, late polymerization, neurological deficits, occluded catheter, passage of embolic material into normal vessels adjacent to the lesion, pulmonary embolism, seizure, stroke or cerebral infarction, thromboembolism, vasospasm, vessel dissection, and vessel perforation.

Primary Effectiveness Results

The primary effectiveness outcome was the degree of vascular occlusion (percent nidus/lesion reduction and number of vessels occluded). Staged embolizations (more than one embolization procedure per patient) were allowed. The mean percent reduction in lesion volume and the mean number of feeding vessels occluded per patient and per stage are listed in Table 2.

Secondary Effectiveness/Safety Results

Additional parameters assessed included the time of resection and the blood volume replacement needed (units of blood, fluid/colloid, or amount from autologous blood recovery device.) Results for the time of resection and blood volume replacement are reported in Table 3.

Table 1
Incidence of Complications

Complications	**n-BCA (N=54)**	**PVA (N=52)**
Seizure	5 (9.3%)	5 (9.6%)
Catheter glued inside vessel	4 (7.4%)	0 (0.0%)
Late Polymerization	3 (5.6%)	0 (0.0%)
Occluded Catheter	3 (5.6%)	5 (9.6%)
Parenchymal hemorrhage	3 (5.6%)	6 (11.5%)
Vasospasm	3 (5.6%)	7 (13.5%)
AVM rupture	2 (3.7%)	1 (1.9%)
Early Polymerization	2 (3.7%)	0 (0.0%)
Inability to subselect vessel	2 (3.7%)	4 (7.7%)
CVA (stroke)	2 (3.7%)*	3 (5.8%)
Death	1 (1.9%)	3 (5.8%)
Hematoma	1 (1.9%)	1 (1.9%)
Incorrect vessel(s) occluded	1 (1.9%)*	0 (0.0%)

Infection/Inflammation	1 (1.9%)	0 (0.0%)
Over-the-wire system could not be advanced	1 (1.9%)	1 (1.9%)
Thromboembolism	1 (1.9%)	1 (1.9%)
Vessel dissection	1 (1.9%)	1 (1.9%)
Vessel perforation	1 (1.9%)	3 (5.8%)
Cranial ischemia (TIA)	0 (0.0%)	2 (3.8%)
Catheter rupture	0 (0.0%)	1 (1.9%)
Failure to access vessel	0 (0.0%)	2 (3.8%)
Flow too high for safe infusion of embolic agent	0 (0.0%)	2 (3.8%)
Headache	0 (0.0%)	2 (3.8%)
Pulmonary embolism	0 (0.0%)	1 (1.9%)
Subarachnoid hemorrhage	0 (0.0%)	2 (3.8%)
Subject failed provocative test	0 (0.0%)	1 (1.9%)
Subject uncooperative	0 (0.0%)	2 (3.8%)
Other	9 (17.3%)*	9 (17.3%)

**One patient (n-BCA) was discontinued from the clinical trial due to an unanticipated adverse device effect. A small amount of glue refluxed into the proximal middle cerebral artery and embolized into branches of the middle cerebral artery. The patient developed a neurologic deficit with aphasia and hemiparesis. This event resulted in permanent disability and the patient was determined not to be an appropriate surgical candidate due to neurological status.*

Table 2 Lesion Volume Reduction and Feeder Vessel Occlusion per Patient and per Stage, by Treatment				
	Patient		Stage	
	n-BCA	PVA	n-BCA	PVA
Mean Percent Reduction In Lesion Volume	79.4 (N=47)	86.9 (N=47)	81.1 (N=71)	79.9 (N=76)
Mean Number of Feeding Vessels Occluded	2.2 (N=48)	2.1 (N=45)	1.5 (N=72)	1.3 (N=72)

The value of N provided in parentheses represents the number of patients or stages without missing data that were used for the effectiveness analyses.

Table 3 Summary of Data During Surgery – Time to Resect AVM and Volume Blood Replacement Needed			
	n-BCA[1](N=52)	PVA[2] (N=49)	Total (N=101)
Was AVM resected?			
Yes	49 (92.5%)	48 (92.3%)	97 (92.4%)
No[3]	4 (7.5%)	4 (7.7%)	8 (7.6%)
Time to resect AVM (min.)			
N	47	46	93
Mean	393.9	401.3	397.5
Median	373.0	357.5	365.0
Volume Replacement Needed: Units of blood or blood product			
N	47	44	91
Mean	1.1	3.1	2.0
Volume Replacement Needed: Fluid/colloid (mL)			
N	47	47	94
Mean	3683	3597	3640
Volume Replacement Needed: Amount from autologous blood recovery device (mL)			
N	41	40	81
Mean	48.8	181.8	114.4

[1]*One n-BCA patient underwent multiple resections.*

[2]*Two PVA patients underwent multiple resections. One patient had an aborted resection after the dura was opened, then underwent true resection at a later date.*

[3] *One crossover patient (PVA to n-BCA) was not resected.*

Note: Column headings show number of patients; however, percentages are based on total number of procedures, a total of 105 (53 n-BCA and 52 PVA).

Table 4 Recommended Mixtures (Listed volumes based on a total volume of 1.0 mL actual total volumes may vary)			
Conditions	**TRUFILL Ethiodized Oil: n-BCA Ratio (EO: n-BCA)**	**TRUFILL Ethiodized Oil Volume (mL)**	**TRUFILL n-BCA Volume (mL)**
Intranidal injections without AV fistulae or high flow rates, in order to more deeply penetrate the nidus	3:1 (75% EO/25% n-BCA)	0.75	0.25
	2:1 (67% EO/33% n-BCA)	0.67	0.33
Feeding pedicle injections close to the nidus, at high flow rates where venous opacification occurs on contrast injections within 0.5 second	1:1 (50% EO/50% n-BCA	0.50	0.50*
	1:2 (33% EO/67% n-BCA	0.33	0.67*
	*TRUFILL Tantalum Powder may also be added to Ethiodized Oil to augment radiopacity. Tantalum powder should not be used alone with n-BCA. At higher n-BCA concentrations (>50%), addition of up to 0.5 g tantalum powder is advised.		

Subdural Hematoma clinical trial

Note: The clinical data presented include patients enrolled in both surgical and non-surgical cohorts per the approved clinical protocol. Data from both cohorts were used to support the overall clinical evaluation. The approved indication is embolization of the Middle Meningeal Artery (MMA) for the treatment of symptomatic subacute or chronic Subdural Hematoma (SDH) as an adjunct to surgery.

Study Design

The study is titled “Middle Meningeal Artery EMbolization for the Treatment of SuBduRal HemAtomas with TRUFILL n-BCA” (MEMBRANE).

The objective of this study was to evaluate the safety and effectiveness of TRUFILL n-BCA for embolization of the Middle Meningeal Artery (MMAE) in patients presenting with a subacute or chronic Subdural Hematoma (SDH) compared to patients treated with standard of care. This study was a prospective, multi-center, open-label, randomized controlled study that enrolled 376 adults at 33 sites in the US and China.

The study stratified enrollment by patients that were treated with surgery, with and without adjunctive embolization (surgical cohort), and those that were treated with non-surgical medical management (NSMM), with and without adjunctive embolization (non-surgical cohort). Data from the two cohorts were pooled and used in support of approval of the device as an adjunct to surgery.

The control group received standard of care (SOC) treatment consisting of either surgical management alone (burr hole evacuation, craniotomy, or other surgical procedures) for the surgical cohort, or NSMM alone (medication management, observation, lifestyle modifications) for the non-surgical cohort. The test group received SOC treatment (surgery or NSMM) in addition to MMAE with the TRUFILL n-BCA LES. Patients in the surgical cohort who were randomized to the test arm underwent MMAE within 10 days after the surgical procedure and within the same hospital admission. Crossover was not permitted between the randomized arms, or between the surgical cohort and the observational cohort.

Subjects were followed procedurally and at 1 month, 3 months, 6 months, and 1 year post-procedure.

Patients presenting with a SDH were assessed by the institution's neurological team to determine the appropriate SOC treatment regardless of the research study, either surgical or non-surgical medical management. Patients were then screened for trial enrollment based on the protocol inclusion and exclusion criteria. Patients who met all eligibility criteria and consented to participate in the MEMBRANE study were randomized 1:1 to undergo MMAE plus SOC vs SOC alone (either surgical or non-surgical management). Patients in the surgical cohort who were randomized to the test arm underwent MMAE within 10 days after the surgical procedure and within the same hospital admission. Crossover was not permitted between the randomized arms, or between the surgical cohort and the observational cohort.

The primary effectiveness endpoint was residual or re-accumulation of the SDH (>10 mm) at 6 months as assessed by an Independent Core Laboratory or re-operation or surgical procedure on the SDH within 6 months post-randomization. The primary endpoint was evaluated as a superiority analysis of the test group (MMAE + SOC) to the control group (SOC alone). The endpoint was evaluated at a one-sided significance level of 0.05 using a Cochran-Mantel-Haenszel (CMH) common odds ratio.

The primary safety endpoint was occurrence of all AEs through 6 months which was evaluated descriptively.

The protocol pre-specified three hypothesis-driven secondary endpoints which were to be conducted hierarchically pending a successful primary endpoint outcome and pending success of the prior hierarchy level. The first hypothesis-driven secondary endpoint was good functional outcome at 3 months (mRS 0-2 or no worsening from baseline if baseline mRS ≥3). The second and third hypothesis-driven secondary endpoints included incidence of patients requiring surgical procedures on the SDH within 12 months and mean change in hematoma volume at 12 months with respect to baseline. Data from the second and third hypothesis

driven secondary endpoints were not available at the time of labeling generation and therefore are not presented herein.

Key Inclusion Criteria

- Age 18 – 90 years at time of consent.
- Diagnosis of chronic subdural hematoma with mass effect
- Pre-randomization modified Rankin Scale (mRS) ≤ 3.
- Subdural Hematoma Size:
  Non-Surgical Medical Management Cohort:
  - Midline shift < 10 mm and hematoma thickness > 10 mm as measured on coronal image perpendicular to the skull.
  - No focal deficit related to the SDH.

  Surgical Cohort – no requirement.
- CT performed within 36 hours prior to randomization demonstrates stability of hematoma. Stability is defined as no worsening of midline shift or increase in SDH size from screening image that results in new or worsening clinical symptoms.
- In the opinion of the treating physician, treatment with TRUFILL n-BCA is technically feasible (e.g., no significant vessel tortuosity, stenosis, occlusion, variation in vascular anatomy to prohibit safe endovascular access.)
- Patient or Legal Authorized Representative confirmed the subject has the mental capacity, willingness and ability to comply with protocol and follow-up requirements.

Key Exclusion Criteria

- Acute SDH, e.g., patient with a SDH due to trauma (mixed density is permitted).
- History of craniotomy/burr hole/Subdural Evacuation Port System (SEPS) ipsilateral to SDH prior to the baseline procedure treatment.
- Bilateral SDH (contralateral SDH <5mm and not requiring treatment permitted)
- Glasgow Coma Scale (GCS) < 9.
- Markwalder Grading Scale (MGS) assessment ≥ 3.
- SDH with underlying conditions such as vascular lesions, brain tumor, arachnoid cyst, spontaneous intracranial hypotension, end stage renal disease on hemodialysis, end stage liver disease, or other comorbidities causing coagulopathy.
- Prior carotid stent placement that crosses the origin of the External Carotid Artery (ECA) ipsilateral to the subdural hematoma.
- Selective angiography demonstrates opacification of a potentially dangerous anastomosis or dangerous anatomic variation that could lead to increased procedural risk.
- Life expectancy of less than 1 year.
- Presumed septic embolus, or suspicion of microbial superinfection.
- CT or MRI evidence of intra-cranial tumor or mass lesion.
- Significant contraindication to angiography (e.g., kidney failure).
- Women who were pregnant, lactating, or who were of childbearing age and planned on becoming pregnant during the course of the clinical investigation.

- Current involvement in an investigational (drug, device, etc.) clinical trial that may have confounded study endpoints; subjects in observational, natural history, and/or epidemiological studies not involving intervention were eligible; Sponsor approval was required prior to randomization.
- Subject unwilling to follow SOC recommendations (e.g., refused surgery or lifestyle modifications).

Patient Accounting

At the time of database lock, 390 patients enrolled in the MEMBRANE study of which 376 subjects were randomized including 188 test subjects. (133 MMAE + surgery, 55 MMAE+ NSMM) and 188 control subjects (132 surgery alone, 56 NSMM alone). Of the subjects that were consented but not randomized, 11 failed to meet eligibility criteria and 3 withdrew prior to randomization. The following analysis populations were defined and used in the protocol:

Intent-to-Treat (ITT) Analysis Set: This set includes all enrolled subjects who were randomized in the study. Subjects were analyzed as randomized regardless of treatment received.

Per Protocol (PP) Analysis Set: This set is a subset of the ITT analysis set, excluding the subjects with significant eligibility deviations, as well as those who did not receive treatment as assigned, in addition to other major protocol deviations which were outlined in the SAP.

As Treated (AT) Analysis Set: This set includes all subjects randomized in the study who received study treatment. Subjects were analyzed by actual treatment they received.

Of the enrolled subjects, 303 subjects completed the 6-month visit and 277 (73.7%) patients had primary endpoint data at the 6-month post-operative visit.

Reasons for not completing the 6-month visit were death prior to completion of 6-month visit in 22 subjects (5.9%), withdrawal by subject in 21 (5.6%), relocation in 1 (0.3%), whereas 29 (7.7%) were ongoing but did not perform a 6-month visit.

Additionally, 8 subjects in the test arm (4 in the surgical cohort and 4 in the non-surgical cohort) did not receive the TRUFILL LES. In the control arm, 15 subjects did not receive their assigned treatment (9 in the surgical cohort and 6 in the non-surgical cohort).

Demographics

Demographic characteristics for subjects in the MEMBRANE clinical trial are summarized in Table 5.

Table 5
Demographics and Baseline Characteristics

Category	TRUFILL+SOC N=188	SOC Alone N=188
Age at consent (years), Mean (Standard Deviation)	70.9 (10.64)	70.3 (12.05)
Gender, Female, n/N* (%)	45/188 (23.9)	49/188 (26.1)
Ethnicity, n/N* (%)		
Hispanic or Latino	15/188 (8.0)	11/188 (5.9)
Not Hispanic or Latino	171/188 (91.0)	173/188 (92.0)
Not reported	2/188 (1.1)	4/188 (2.1)
Race, n/N* (%)		
American Indian or Alaska Native	0/188 (0.0)	1/188 (0.5)
Asian	18/188 (9.6)	17/188 (9.0)
Black or African American	29/188 (15.4)	26/188 (13.8)
Native Hawaiian or other Pacific Islander	0/188 (0.0)	0/188 (0.0)
White	124/188 (66.0)	128/188 (68.1)
Not Reported	15/188 (8.0)	16/188 (8.5)
Other	2/188 (1.1)	0/188 (0.0)
Multi-racial	0/188 (0.0)	0/188 (0.0)
Modified Rankin Score (mRS), n/N* (%)		
0-2	141/188 (75.0)	145/188 (77.1)
3	47/188 (25.0)	43/188 (22.9)
Hypertension, n/N (%)	124/188 (66.0)	138/188 (73.4)
Current Smoker, n/N (%)	22/188 (11.7)	18/188 (9.6)
Chronic Alcoholism, n/N (%)	24/188 (12.8)	19/188 (10.1)
Prior ischemic stroke, n/N (%)	20/188 (10.6)	14/188 (7.4)
Antiplatelet and/or Anticoagulant Medication at Symptom Onset[1], n/N (%)		
Antiplatelet Medication Only	3/188 (1.6)	8/188 (4.3)
Anticoagulant Medication Only	68/188 (36.2)	34/188 (18.1)
Antiplatelet and Anticoagulant Medication	2/188 (1.1)	4/188 (2.1)

n = number of subjects with data available by category; N = number of subjects in the analysis set.
Note: Denominator (N) of the percentage is based on the number of subjects with non-missing values.*
Note: Denominator (N) of the percentage is based on the number of subjects in the analysis set.
[1]Antiplatelet and/or anticoagulant medications that were taken at the time of randomization (medication start date on or prior to the randomization date and medication end date on or after the randomization date).

Baseline Chronic Subdural Hematoma Characteristics

Baseline SDH characteristics per Independent Core Lab for subjects in the MEMBRANE clinical trial are summarized in Table 6.

Table 6
Target Chronic Subdural Hematoma Baseline Characteristics

Category	TRUFILL+SOC N=188	SOC Alone N=188
Presence of an acute component, n/N (%)	160/187 (85.6)	157/185 (84.9)
Anatomic side of SDH, n/N* (%)		
Bilateral	20/188 (10.6)	27/188 (14.4)
Unilateral	168/188 (89.4)	161/188 (85.6)
Volume of hematoma (cm3), Mean (Standard Deviation)	69.95 (41.083)	76.47 (43.542)
Thickness of hematoma (mm), Mean (Standard Deviation)	15.19 (5.097)	15.06 (5.110)
Midline shift (mm), Mean (Standard Deviation)	4.70 (3.311)	4.51 (2.879)
Headache, n/N (%)	122/188 (64.9)	128/188 (68.1)
Memory Loss or Confusion, n/N (%)	77/188 (41.0)	75/188 (39.9)
Dysarthria or Aphasia, n/N (%)	53/188 (28.2)	40/188 (21.3)
Gait Impairment / Instability, n/N (%)	79/188 (42.0)	86/188 (45.7)
Limb Weakness, n/N (%)	90/188 (47.9)	91/188 (48.4)
Baseline MGS, Mean (Standard Deviation)	1.0 (0.63)	1.0 (0.65)
Baseline mRS, Mean (Standard Deviation)	1.59 (1.038)	1.55 (0.982)

n = number of subjects with data available by category; N = number of subjects in the analysis set.
Note: Denominator (N) of the percentage is based on the number of subjects with non-missing values.*
Note: Denominator (N) of the percentage is based on the number of subjects in the analysis set.

Treatment and Procedural Details

Treatment and procedural details for subjects in the MEMBRANE clinical trial are summarized in Table 7.

Table 7
Treatment and Procedural Details

Category	TRUFILL+ Surgery N=133	TRUFILL + NSMM N=55
Side treated, n/N* (%)		
Left	60/133 (45.1)	22/55 (40.0)
Right	58/133 (43.6)	29/55 (52.7)
Bilateral	15/133 (11.3)	4/55 (7.3)
MMAE Procedural time (minutes), Mean (Standard Deviation)	71.1 (31.99)	71.5 (33.65)
Surgical Procedure type, n/N* (%)		
Craniotomy	47/133 (35.3)	Not applicable
Burr-hole Evacuation	95/133 (71.4)	Not applicable
Vascular access, n/N* (%)		
Radial artery	56/129 (43.4)	26/51 (51.0)
Femoral artery	73/129 (56.6)	25/51 (49.0)

n = number of subjects with data available by category; N = number of subjects in the analysis set.
Note: Denominator (N) of the percentage is based on the number of subjects with non-missing values.*

Adverse Events

Table 8 lists site reported adverse events in the AT analysis set through 6-month follow-up with > 1% overall frequency in either treatment arm for adverse events in the System Organ Class

of “Nervous system disorders” and > 1% overall frequency in the embolization treatment groups only for adverse events in all other system organ classes.

Table 8
Summary of Adverse Events (AEs) for MEMBRANE Clinical Study by Medical Dictionary for Regulatory Activities (MedDRA)

	TRUFILL+SOC N=181	**SOC Alone N=190**
System Organ Class (SOC) Preferred Term (PT)	**Number of subjects n/N (%)**	**Number of subjects n/N (%)**
Nervous system disorders		
Headache	23/181 (12.7)	15/190 (7.9)
Dizziness	11/181 (6.1)	5/190 (2.6)
Seizure	9/181 (5.0)	4/190 (2.1)
Partial seizures	4/181 (2.2)	3/190 (1.6)
Aphasia	3/181 (1.7)	3/190 (1.6)
Dysarthria	3/181 (1.7)	0/190 (0.0)
Hypoaesthesia	3/181 (1.7)	4/190 (2.1)
Amnesia	2/181 (1.1)	2/190 (1.1)
Cerebral infarction	2/181 (1.1)	3/190 (1.6)
Generalised tonic-clonic seizure	2/181 (1.1)	0/190 (0.0)
Metabolic encephalopathy	2/181 (1.1)	0/190 (0.0)
Tremor	2/181 (1.1)	1/190 (0.5)
VIth nerve paralysis	2/181 (1.1)	0/190 (0.0)
Encephalopathy	1/181 (0.6)	4/190 (2.1)
Facial paralysis	1/181 (0.6)	2/190 (1.1)
Lethargy	1/181 (0.6)	2/190 (1.1)
Head discomfort	0/181 (0.0)	2/190 (1.1)
Infections and infestations		
Urinary tract infection	14/181 (7.7)	8/190 (4.2)
COVID-19	11/181 (6.1)	10/190 (5.3)
Pneumonia	3/181 (1.7)	5/190 (2.6)
Diverticulitis	2/181 (1.1)	0/190 (0.0)
Septic shock	2/181 (1.1)	0/190 (0.0)

Table 8
Summary of Adverse Events (AEs) for MEMBRANE Clinical Study by Medical Dictionary for Regulatory Activities (MedDRA)

	TRUFILL+SOC N=181	SOC Alone N=190
System Organ Class (SOC) Preferred Term (PT)	**Number of subjects n/N (%)**	**Number of subjects n/N (%)**
Injury, poisoning and procedural complications		
Subdural haematoma	11/181 (6.1)	23/190 (12.1)
Fall	5/181 (2.8)	5/190 (2.6)
Buttock injury	2/181 (1.1)	1/190 (0.5)
Head injury	2/181 (1.1)	1/190 (0.5)
Pneumocephalus	2/181 (1.1)	1/190 (0.5)
Radius fracture	2/181 (1.1)	0/190 (0.0)
Skin injury	2/181 (1.1)	0/190 (0.0)
Vascular access site haematoma	2/181 (1.1)	0/190 (0.0)
General disorders and administration site conditions		
Physical deconditioning	8/181 (4.4)	5/190 (2.6)
Pyrexia	6/181 (3.3)	4/190 (2.1)
Fatigue	4/181 (2.2)	1/190 (0.5)
Chest pain	3/181 (1.7)	4/190 (2.1)
Asthenia	2/181 (1.1)	2/190 (1.1)
Gait disturbance	2/181 (1.1)	2/190 (1.1)
Gastrointestinal disorders		
Vomiting	5/181 (2.8)	2/190 (1.1)
Constipation	4/181 (2.2)	6/190 (3.2)
Abdominal pain	3/181 (1.7)	3/190 (1.6)
Diarrhoea	3/181 (1.7)	1/190 (0.5)
Haematochezia	3/181 (1.7)	0/190 (0.0)
Dysphagia	2/181 (1.1)	0/190 (0.0)

Table 8
Summary of Adverse Events (AEs) for MEMBRANE Clinical Study by Medical Dictionary for Regulatory Activities (MedDRA)

	TRUFILL+SOC N=181	SOC Alone N=190
System Organ Class (SOC) Preferred Term (PT)	**Number of subjects n/N (%)**	**Number of subjects n/N (%)**
Musculoskeletal and connective tissue disorders		
Arthralgia	5/181 (2.8)	8/190 (4.2)
Muscular weakness	4/181 (2.2)	2/190 (1.1)
Back pain	2/181 (1.1)	0/190 (0.0)
Musculoskeletal chest pain	2/181 (1.1)	1/190 (0.5)
Cardiac disorders		
Atrial fibrillation	4/181 (2.2)	0/190 (0.0)
Acute myocardial infarction	3/181 (1.7)	3/190 (1.6)
Tachycardia	3/181 (1.7)	0/190 (0.0)
Cardiac failure	2/181 (1.1)	3/190 (1.6)
Cardiac failure congestive	2/181 (1.1)	3/190 (1.6)
Metabolism and nutrition disorders		
Hypokalaemia	6/181 (3.3)	2/190 (1.1)
Hyponatraemia	3/181 (1.7)	3/190 (1.6)
Hypocalcaemia	2/181 (1.1)	0/190 (0.0)
Hypoglycaemia	2/181 (1.1)	2/190 (1.1)
Psychiatric disorders		
Insomnia	5/181 (2.8)	5/190 (2.6)
Confusional state	3/181 (1.7)	2/190 (1.1)
Anxiety	2/181 (1.1)	0/190 (0.0)
Depression	2/181 (1.1)	1/190 (0.5)

Table 8
Summary of Adverse Events (AEs) for MEMBRANE Clinical Study by Medical Dictionary for Regulatory Activities (MedDRA)

	TRUFILL+SOC N=181	SOC Alone N=190
System Organ Class (SOC) **Preferred Term (PT)**	**Number of subjects** **n/N (%)**	**Number of subjects** **n/N (%)**
Respiratory, thoracic and mediastinal disorders		
Cough	4/181 (2.2)	2/190 (1.1)
Oropharyngeal pain	3/181 (1.7)	0/190 (0.0)
Respiratory failure	3/181 (1.7)	4/190 (2.1)
Pulmonary embolism	2/181 (1.1)	1/190 (0.5)
Renal and urinary disorders		
Urinary retention	5/181 (2.8)	4/190 (2.1)
Acute kidney injury	3/181 (1.7)	4/190 (2.1)
Vascular disorders		
Hypertension	4/181 (2.2)	1/190 (0.5)
Hypotension	3/181 (1.7)	3/190 (1.6)
Deep vein thrombosis	2/181 (1.1)	1/190 (0.5)
Blood and lymphatic system disorders		
Anaemia	4/181 (2.2)	4/190 (2.1)
Thrombocytopenia	3/181 (1.7)	0/190 (0.0)
Skin and subcutaneous tissue disorders		
Rash	2/181 (1.1)	1/190 (0.5)
Ear and labyrinth disorders		
Vertigo	3/181 (1.7)	0/190 (0.0)
Cerumen impaction	2/181 (1.1)	0/190 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Lipoma	2/181 (1.1)	0/190 (0.0)

Table 8
Summary of Adverse Events (AEs) for MEMBRANE Clinical Study by Medical Dictionary for Regulatory Activities (MedDRA)

	TRUFILL+SOC N=181	SOC Alone N=190
System Organ Class (SOC) **Preferred Term (PT)**	**Number of subjects** **n/N (%)**	**Number of subjects** **n/N (%)**
Reproductive system and breast disorders		
Benign prostatic hyperplasia	2/181 (1.1)	0/190 (0.0)

n = number of subjects with data available by category; N = number of subjects in the analysis set.
Note: Denominator (N) of the percentage is based on the number of subjects in the analysis set.
Note: Adverse events that started on or after the date of unplanned embolic treatment in subjects who received unplanned embolic treatment during follow-up (beyond 10 days post randomization or surgery), were excluded from the randomization assignment in the summary table.

Primary Effectiveness Results

The primary effectiveness endpoint was residual or re-accumulation of the SDH (>10 mm) at 6 months as assessed by an Independent Core Laboratory or re-operation or surgical procedure on the SDH within 6 months post-randomization. In the test group, 106 surgical cohort subjects and 40 NSMM subjects contributed to the primary effectiveness endpoint. In the control group, 94 surgical cohort subjects and 37 NSMM subjects contributed to the primary effectiveness endpoint. Multiple imputation was used to impute missing data for subjects with missing primary endpoint data at 6 months (e.g., due to early withdrawal from the study, loss to follow up, or death). As shown in Table 9, the primary analysis resulted in an odds ratio of 0.475 (90% CI: 0.239, 0.944) for the surgical cohort favoring the TRUFILL n-BCA LES, and an odds ratio of 0.615 (90% CI: 0.266, 1.419) for the non-surgical cohort, where the upper confidence interval exceeded 1 which failed to meet significance. As shown in Table 10, the final combined estimate of the common odds ratio was 0.529 (90% CI: 0.308, 0.909) with a one-sided p-value of 0.044. Therefore, the primary effectiveness endpoint was met for the overall population.
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Table 11 shows the reasons for primary effectiveness outcome events in the surgical cohort and the combined cohort (surgical + NSMM). Of note, 3/104 (2.9%) subjects in the test group and 7/86 (8.1%) subjects in the control group within the surgical cohort required re-operation or additional surgical procedures by 6 months which was the most common primary endpoint event in the control group. Additionally, 6/104 (5.8%) subjects in the test group and 3/86 (3.5%) subjects in the control group within the surgical cohort had primary effectiveness endpoint events due to residual or re-accumulation of the SDH (>10 mm). Of note, data presented in “event by reason” rows of Table 11 excludes patients that did not receive their treatment assignment, including several control patients that received a liquid embolic. These trends were similar in the combined cohort.

A sensitivity analysis was conducted using the PP and AT analysis sets. Importantly, the PP analysis set excluded 8 subjects in the test arm that did not receive the TRUFILL LES and 15 subjects in the control arm that did not receive their assigned treatment. The analysis on the PP analysis set resulted in a common OR of 0.776 (90% CI: 0.419, 1.437) for the combined cohort which did not meet significance for the primary endpoint and raises questions regarding the robustness of the estimate of the primary endpoint. However, analysis of the combined cohort on the AT analysis set, which analyzes subjects per the treatment received regardless of treatment assignment

showed significance favoring the test group with a common OR of 0.426 (90% CI: 0.244, 0.743).

Table 9
Primary Effectiveness Endpoint by Cohort

Category	**Surgical Cohort** N=265	**NSMM Cohort** N=111
Primary effectiveness endpoint at 6 months		
Estimate of odds ratio with imputed data (90% CI)	0.475 (0.239, 0.944)	0.615 (0.266, 1.419)
Note: Odds ratio is defined as the ratio of the odds of event (failure) probability to event-free (success) probability in subjects with MMAE procedure vs. those without MMAE procedure. An OR <1 favors the treatment with MMAE of less likelihood of primary effectiveness endpoint event.		

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Table 10
Primary Effectiveness Endpoint

Category	**TRUFILL+SOC N=188**	**SOC Alone N=188**	**Overall N=376**
Primary effectiveness endpoint at 6 months with observed data, n/N (%)	17/146	29/131	
Combined estimate for common odds ratio with imputed data			0.529
90% CI (Mantel Haenszel method)			(0.308,0.909)
p-value of one-sided Cochran-Mantel-Haenszel (CMH) test			0.044
Note: Common odds ratio is defined as the ratio of the odds of event (failure) probability to event-free (success) probability in subjects with MMAE procedure vs. those without MMAE procedure. An OR <1 favors the treatment with MMAE of less likelihood of primary effectiveness endpoint event.			

Table 11
Primary Effectiveness Endpoint by Reason

	Surgical Cohort		**Combined Cohort**	
Category	**TRUFILL + Surgery**	**Surgery Alone**	**TRUFILL + SOC**	**SOC Alone**
Primary effectiveness endpoint at 6 months, n/N* (%)	9/106 (8.5)	19/94 (20.2)	17/146 (11.6)	29/131 (22.1)

Category	Surgical Cohort		Combined Cohort	
	TRUFILL + Surgery	Surgery Alone	TRUFILL + SOC	SOC Alone
Missing data, n	27	38	42	57
Event by reason⁺, n/N* (%)				
Due to residual or re-accumulation of the SDH (>10mm) per independent core lab at 6 months	6/104 (5.8)	3/86 (3.5)	10/143 (7.0)	6/119 (5.0)
Due to re-operation or surgical procedure on the SDH within 6 months	3/104 (2.9)	7/86 (8.1)	6/143 (4.2)	10/119 (8.4)
Due to embolic treatment (Trufill n-BCA or non-Trufill n-BCA) other than index procedure prior to 6-month	0/104 (0.0)	0/86 (0.0)	0/143 (0.0)	0/119 (0.0)
Due to death related to study device (Trufill n-BCA) or due to underlying disease status within 6 months per CEC	0/104 (0.0)	2/86 (2.3)	0/143 (0.0)	2/119 (1.7)

CEC = clinical events committee; SDH = chronic subdural hematoma; n = number of subjects by endpoint; N =number of subjects in the analysis set; SOC = standard of care surgery or NSMM.
Note: Primary effectiveness endpoint event is defined as residual or re-accumulation of the SDH (>10 mm) at 6 months per independent core laboratory or re-operation or surgical procedure on the SDH within 6 months post randomization.
Note: A subject may be considered as the primary effectiveness endpoint with one or more events; however, a subject is counted once in each category.
Note: Denominator (N*) for the percentage is based on the number of subjects with non-missing values of the primary effectiveness endpoint.
⁺ Denominator is based on the number of subjects that received their assigned treatment without any crossover

Subgroup analyses

The following baseline characteristics were evaluated for potential association with the primary effectiveness outcome: ethnicity, race, age, sex and region and site homogeneity. Significant differences among subgroups were not identified. Subgroup analyses were exploratory in nature and should be interpreted with caution, as the study was not specifically powered for subgroup comparisons.

Primary Safety Endpoint

The primary safety endpoint was overall incidence of AEs through 6 months and was based on the AT analysis set of 371 patients available through the 6-month evaluation. Within the AT analysis set, 414 AEs occurred in 130/181 (71.8%) subjects in the test arm and 392 AEs occurred in 124/190 (65.3%)

subjects in the control arm. Table 12 presents the overall incidence of adverse events by seriousness, severity, and relation through 6 months within the ITT analysis set, excluding subjects who did not receive their treatment assignment. Of the 180 subjects in the test arm that received TRUFILL LES, 12/180 (6.7%) subjects experienced AEs related to the device and 1/180 (0.6%) subject experienced an SAE (cerebral artery infarct) related to the device. The most common device related AE was seizure which occurred in 11/180 (6.1%) subjects. In addition, 4/180 (2.2%) subjects experienced SAEs related to the embolization procedure. A total of 2/180 (1.1%) patients experienced unintended vessel occlusion, and 4/180 (2.2%) subjects experienced vascular access site complications. Catheter entrapment was not observed in any subjects receiving TRUFILL LES. Table 13 presents neurological deaths and neurological events of interest through 6 months within the ITT analysis set, excluding subjects that did not receive their treatment assignment. No neurologic deaths associated with the device or embolization procedure were observed. Overall, the use of the TRUFILL LES did not present any unknown risks that have not been previously described.

Table 12
Overall Incidence of Adverse Events by Seriousness, Severity, and Relation through 6 months

Category	TRUFILL+SOC N=188 Number of subjects n/N* (%)	SOC Alone N=188 Number of subjects n/N* (%)
All AEs (including SAEs, non-SAEs)	129/180 (71.7)	110/173 (63.6)
Non-SAEs	110/180 (61.1)	95/173(54.9)
Serious adverse events (SAEs)	50/180 (27.8)	49/173 (28.3)
SAEs Related to Embolization Procedure through 6 months	4/180 (2.2)	Not Applicable
SAEs Related to TRUFILL through 6 months	1/180 (0.6)	Not Applicable
AEs Related to TRUFILL through 6 months	12/180 (6.7)	Not Applicable
Severe AEs through 6 months	24/180 (13.3)	32/173 (18.5)
Unintended Vessel Occlusion	2/180 (1.1)	Not Applicable
Catheter Entrapment	0/180 (0.0)	Not Applicable
Access Site Complications	4/180 (2.2)	Not Applicable
TRUFILL LES Migration	0/180 (0.0)	Not Applicable

n = number of subjects with data available by category; N = number of subjects in the analysis set.
Note: Denominator (N) of the percentage is based on the number of subjects that received their assigned treatment without any crossover.*

Table 13
Neurologic Death and Neurologic Events of Interest through 6 Months

Category	TRUFILL+SOC N=188 Number of subjects n/N* (%) [Number of events]	SOC Alone N=188 Number of subjects n/N* (%) [Number of events]
All Neurologic Deaths[1]	3/180 (1.7) [3]	4/173 (2.3) [4]
Related to Study Device[1]	0/180 (0.0) [0]	0/173 (0.0) [0]
Related to Embolization Procedure[1]	0/180 (0.0) [0]	0/173 (0.0) [0]
Related to Surgery Procedure[1,2]	0/129 (0.0) [0]	4/123 (3.0) [4]
Related to SDH Medication[1]	0/180 (0.0) [0]	0/173 (0.0) [0]
Other[3]	3/180 (1.7) [3]	0/173 (0.0) [0]
Stroke[1]	3/180 (1.7) [3]	2/173 (1.2) [2]
Cerebral Infarction	2/180 (1.1) [2]	2/173 (1.2) [2]
Serious Intracranial Hemorrhage	2/180 (1.1) [2]	7/173 (4.0) [7]
New onset of seizures[1]	11/180 (6.1) [11]	6/173 (3.5) [6]
TIA	1/180 (0.6) [1]	0/173 (0.0) [0]
Ipsilateral Visual Symptoms	2/180 (1.1) [2]	1/173 (0.6) [1]

n = number of subjects with data available by category; N = number of subjects in the analysis set.
Note: Denominator (N) of the percentage is based on the number of subjects that received their assigned treatment without any crossover.*
[1]Neurological deaths and relatedness, stroke, and new onset of seizures were adjudicated by the Clinical Events Committee (CEC), and all other events were site reported.
[2]Denominator is based on the number of patients receiving surgery.
[3]Other relatedness is defined as relatedness not pertaining to study device, embolization procedure, surgery procedure, or SDH medication.

Secondary Effectiveness Endpoint

Good Functional Outcome at 3 Months (mRS 0-2 or No Worsening from Baseline if Baseline mRS ≥3)

An assessment of good functional outcome at 3 months (mRS 0-2 or no worsening from baseline if baseline mRS ≥3) was performed in the ITT analysis set. As shown in Table 14 122/143 (85.3%) of test group subjects and 104/135 (77.0%) of control group subjects had good functional

outcomes at 3 months demonstrating non-inferiority of the test group to the control group with regard to good functional outcome.

Table 14
Good Functional Outcome at 3 months – MMAE Treatment vs. SOC Treatment

Category	**TRUFILL+SOC** n=188	**SOC Alone** N=188
Good functional outcome (mRS 0-2 or no worsening from baseline if baseline mRS ≥ 3) at 3 months with observed data, n/N (%)	122/143 (85.3)	104/135 (77.0)
Combined estimate for risk difference with imputed data		0.073
90% CI		(0.001, 0147)

n = number of subjects by endpoint; N = number of subjects in the analysis set.
Note: Risk difference is calculated as the difference of the event rates of the treatment arm with TRUFILL vs. standard of care arm without TRUFILL.
Note: Denominator (N) of the percentage of the observed data is calculated based on the non-missing value of the endpoint by category.*

Additional analyses:

A post-hoc analysis was completed using a composite endpoint with the following components evaluated at 6 months post-randomization:

(1) Residual or re-accumulation of the SDH compared to baseline hematoma,
(2) AEs of symptomatic subdural hematoma within 6-months,
(3) All-cause mortality within 6-months,
(4) Worsening of the Markwalder Grading Scale (MGS) at 6 months compared to baseline MGS.

The outcomes of this post-hoc analysis are shown in Table 15 for the composite endpoint and each component of the composite endpoint. Within the surgical cohort, each component of the post-hoc endpoint trended favorably for the test group with the exception of worsening in MGS at 6 months compared to baseline.

Table 15

Category	Surgical Cohort		Combined Cohort	
	TRUFILL + Surgery	Surgery Alone	TRUFILL + SOC	SOC Alone
Post hoc effectiveness endpoint at 6 months, n/N* (%)	13/106 (12.3)	26/93 (28.0)	22/146 (15.1)	37/134 (27.6)
Missing data, n	27	39	42	54
Event by reason⁺, n/N* (%)				
Due to worsening in hematoma volume at 6 months compared to baseline	4/104 (3.8)	6/85 (7.1)	7/143 (4.9)	8/122 (6.6)
Due to symptomatic SDH as an AE through 6 months	5/104 (4.8)	10/85 (11.8)	9/143 (6.3)	12/122 (9.8)
Due to all-cause mortality through 6 months	1/104 (1.0)	11/85 (12.9)	6/143 (4.2)	16/122 (13.1)
Due to worsening MGS at 6 months compared to baseline	5/104 (4.8)	1/85 (1.2)	7/143 (4.9)	1/122 (0.1)

CEC = clinical events committee; SDH = chronic subdural hematoma; n = number of subjects by endpoint; N = number of subjects in the analysis set.

Note: Primary effectiveness endpoint event is defined as residual or re-accumulation of the SDH (>10 mm) at 6 months per independent core laboratory or re-operation or surgical procedure on the SDH within 6 months post randomization.

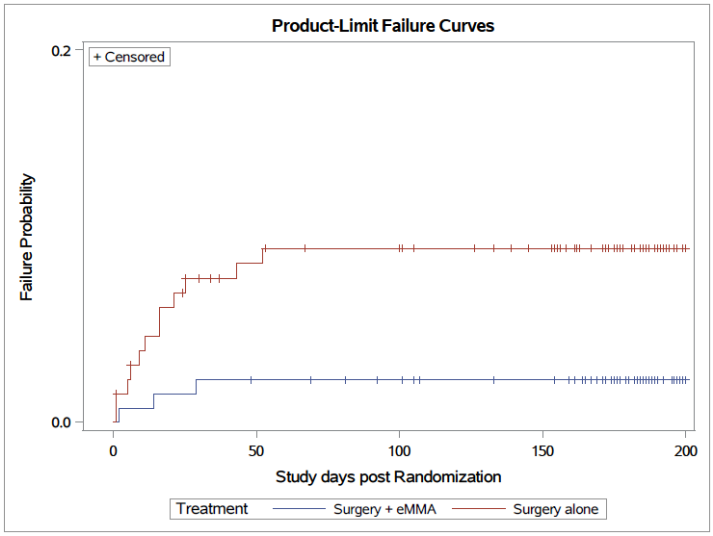
Note: A subject may be considered as the primary effectiveness endpoint with one or more events; however, a subject is counted once in each category.

Note: Denominator (N) for the percentage is based on the number of subjects with non-missing values of the primary effectiveness endpoint.*

⁺Denominator is based on the number of subjects that received their assigned treatment without any crossover.

A Kaplan-Meier analysis of time to surgical procedure on SDH post-randomization was performed. As shown in Figure 2, all post-randomization surgical procedures occurred within 44 days of randomization.

Figure 2
Kaplan-Meier Analysis of Time to Surgical Procedure on SDH post Randomization



Clinical study conclusions

The results of the MEMBRANE study demonstrated that adjunctive use of TRUFILL n-BCA Liquid Embolic System (TRUFILL n-BCA + surgery) is superior in effectiveness compared to surgery alone for embolization in the Middle Meningeal Artery (MMA) for the treatment of SDH in preventing hematoma recurrence/progression requiring surgical drainage. Furthermore, subjects treated with TRUFILL n-BCA Liquid Embolic System as an adjunct to surgery exhibited good functional outcomes, as measured by mRS at three months post-embolization. TRUFILL n-BCA Liquid Embolic System was also demonstrated to be safe for treating SDH, with a safety profile comparable to that of surgery alone. Overall, the findings of the MEMBRANE study indicate that the benefits of TRUFILL n-BCA outweigh the potential risks for the proposed intended use of embolization of the Middle Meningeal Artery (MMA) for the treatment of symptomatic subacute or chronic SDH as an adjunct to surgery.

Warranty

Cerenovus warrants that this medical device is free from defects in both materials and workmanship. Any other express or implied warranties, including warranties of merchantability or fitness, are hereby disclaimed. Suitability for use of this medical device for any particular surgical procedure should be determined by the user in conformance with the manufacturer's instructions for use. There are no warranties that extend beyond the description on the face hereof.

Symbols

Do not resterilize


Do not use if package is damaged


Manufacturer

Made in


Nonpyrogenic

QTY Quantity

Do not reuse

RADIOPAQUE Radiopaque

DO NOT AUTOCLAVE Do not autoclave

Consult instructions for use

Caution

MR Conditional

Keep dry

Keep away from sunlight

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