SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Neurovascular Liquid Embolic Agent

Device Trade Name: TRUFILL n-BCA Liquid Embolic System (LES),
TRUFILL n-BCA Liquid Embolic System Procedural Set

Device Procode: SGU, KGG

Applicant's Name and Address: Cerenovus, Inc.
6303 Waterford District Drive
Suites 215 & 315
Miami, FL 33126 USA

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P990040/S034

Date of FDA Notice of Approval: December 16, 2025

The original PMA P990040 of the TRUFILL n-BCA Liquid Embolic System, was first approved on September 25, 2000, and was indicated for the embolization of cerebral arteriovenous malformations (AVMs) when presurgical devascularization is desired. The SSED to support the indication is available on the following FDA website and is incorporated by reference herein:

https://www.accessdata.fda.gov/cdrh_docs/pdf/P990040B.pdf

The current supplement was submitted to expand the indication for the TRUFILL n-BCA Liquid Embolic System and TRUFILL n-BCA Liquid Embolic System Procedural Set to include embolization of the middle meningeal artery (MMA) as an adjunct to surgery in the treatment of symptomatic subacute and chronic subdural hematoma (SDH).

II. INDICATIONS FOR USE

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.

III. 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.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the TRUFILL n-BCA Liquid Embolic System labeling.

V. DEVICE DESCRIPTION

The TRUFILL n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System (TRUFILL LES) is an artificial embolization device, comprised of TRUFILL n-Butyl Cyanoacrylate (n-BCA), TRUFILL Ethiodized Oil and TRUFILL Tantalum Powder (Figure 1). These components must be used as a system. The TRUFILL Procedural Set includes accessories (syringes (1 and 3ml), needles (blunt fill and hypodermic) and a mixing beaker) which are used to prepare and deliver the implantable components. The device is sold with and without Procedural Set accessories. The TRUFILL LES is designed to be delivered under fluoroscopy to targeted lesions through Cerenovus families of microcatheters (PROWLER and TRANSIT).

The TRUFILL LES is delivered under fluoroscopic guidance to obstruct or reduce blood flow to embolize cerebral arteriovenous malformations (cAVM) 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 Powder is a finely ground, irregularly shaped, dark gray metal that can be used with Ethiodized Oil to make the n-BCA radiopaque.

Figure 1. TRUFILL n-BCA Liquid Embolic System is comprised of n-BCA, Ethiodized Oil, and Tantalum Powder

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of SDH including non-surgical and surgical approaches. Non-surgical approaches include medication to limit or eliminate further bleeding by modifying blood coagulation and clotting, and to withhold blood thinning medications. Alternatively, surgical approaches may include procedures to remove/drain blood from areas within the hematoma and to repair or remove abnormal areas of the neurovasculature that are causing the hematoma and may be conducted during a craniotomy, burr hole surgery, or twist drill craniotomy. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The TRUFILL n-BCA LES is marketed for MMA embolization (MMAE) in the following regions: the European Union (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Iceland, Liechtenstein, and Norway); the United Kingdom, Switzerland, Colombia, and Oman.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- 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
- Fluoroscopy related complications including alopecia, burns ranging in severity from skin reddening to ulcers, cataracts, and delayed neoplasia

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

A summary of previously reported non-clinical studies can be found in the SSED for the original PMA. In addition, the sponsor provided a contemporary toxicological risk assessment for assessing biological endpoints of carcinogenicity. The testing was acceptable to demonstrate the safety of the device with respect to carcinogenicity.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study titled "Middle Meningeal Artery EMbolization for the Treatment of SuBduRal HemAtomas with TRUFILL n-BCA (MEMBRANE)" to establish a reasonable assurance of safety and effectiveness of MMAE with TRUFILL LES for the treatment of symptomatic subacute and chronic SDH in the US and China under IDE # G200310. Data from this clinical study were the basis for the PMA Panel Track Supplement (PTS) approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between May 2021 and February 2024. The database for this Panel Track Supplement reflected data collected through October 2024, and included 376 randomized patients. There were 33 investigational sites.

The study was a prospective, multi-center, open-label, two cohort (surgical and non-surgical), randomized controlled clinical study. 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). The institution's neurological team determined whether a patient was included in the surgical cohort or NSMM cohort. Data from the two cohorts were pooled and used in support of approval of the device as an adjunct to surgery.

Patients who met all eligibility criteria and consented to participate in the MEMBRANE study were randomized 1:1 between test and control arms. 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 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.

The MEMBRANE study utilized an independent imaging core laboratory for blinded assessment of primary and secondary imaging endpoints (SDH volume, thickness, midline shift), qualified independent evaluators blinded to treatment assignment for mRS and MGS scoring at 1-, 3-, 6-, and 12-month visits, a Clinical Events Committee (CEC) for adjudication of safety endpoint events and adverse event causality, and a Data Monitoring Committee (DMC) for periodic safety monitoring and recommendations regarding study continuation.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the MEMBRANE study was limited to patients who met the following inclusion criteria:

1) Subject is between 18 and 90 years of age (inclusive) at the time of consent.
2) Subject had a diagnosis of SDH with mass effect determined by brain imaging (CT or MRI) and correlated clinical symptoms.
3) Pre-randomization mRS <3
    a. Surgical Cohort: Assessment reflected the subject's condition just prior to undergoing surgery. Assessment may have been performed post-surgery using pre-surgical data.
4) SDH Size
    a. NSMM Cohort
        i. Midline shift <10 mm and hematoma thickness >10 mm as measured on coronal imaging perpendicular to the skull.
        ii. No focal deficit related to the SDH.
    b. Surgical Cohort
        i. No requirement.
5) A CT performed within 36 hours prior to randomization demonstrating stability of the hematoma. Stability was defined as no worsening of midline shift or increase in the size of the SDH from the screening image that resulted in new or worsening clinical symptoms.
6) Subject or designated Legal Authorized Representative confirmed the subject had the mental capacity, willingness, and ability to comply with protocol and follow-up requirements.
7) In the opinion of the treating physician, treatment with TRUFILL n-BCA was technically feasible (e.g., no significant vessel tortuosity, stenosis, occlusion or variation in vascular anatomy to prohibit safe endovascular access).

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

1) Subject presented with an acute SDH (e.g., subject presented with a SDH due to trauma); mixed density was permitted.
2) Subject had a prior history of craniotomy/burr hole/Subdural Evacuating Port System (SEPS) ipsilateral to the SDH prior to the baseline procedure treatment.
3) Subject presented with bilateral SDHs (contralateral SDH <5 mm and not requiring treatment was permitted).
4) Subject presented with Glasgow Coma Scale (GCS) <9.
5) Markwalder Grading Scale (MGS) assessment ≥3.
6) SDH that developed 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 a coagulopathy.
7) Prior carotid stent placement that crossed the origin of the external carotid artery (ECA) ipsilateral to the subdural hematoma.

8) Selective angiography demonstrated opacification of a potentially dangerous anastomosis or dangerous anatomic variation that could have led to increased procedural risk.
9) Presumed septic embolus, or suspicion of microbial superinfection.
10) CT or MRI evidence of intra-cranial tumor or mass lesion.
11) Significant contraindication to angiography (e.g., kidney failure).
12) Life expectancy less than 1 year.
13) Women who were pregnant, lactating, or who were of childbearing age and planned on becoming pregnant during the course of the clinical investigation.
14) 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.
15) Subject unwilling to follow SOC recommendations (e.g., refused surgery or lifestyle modifications).

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at Day 0 (within 10 days of surgery/randomization), 1 month (±14 days), 3 months (±14 days), 6 months (±30 days), and 1 year (±60 days) postoperatively. Preoperative and postoperative follow up evaluations include physical and functional assessments, imaging tests, surveys of concomitant medications, and quality of life (QoL) questionnaires. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

Primary Effectiveness Endpoint

The primary effectiveness endpoint was residual or re-accumulation of the SDH (>10mm) 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), for the following hypotheses test:

$$H_0: \theta_{CMH} \geq 1$$
$$H_1: \theta_{CMH} < 1$$

where θ_{CMH} is the Cochran-Mantel-Haenszel common odds ratio (OR) between the test group and the control group for the primary effectiveness endpoint and SOC was either surgery or NSMM. With respect to success, the hypothesis test was evaluated at a one-sided significance level of 0.05 to meet the primary effectiveness endpoint and claim superiority of the test group over the control group.

Primary Safety Endpoint

The primary safety endpoint was the occurrence of all adverse events (AEs) through 6 months which was evaluated descriptively.

Hypothesis Driven Secondary Endpoints

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 is shown below. 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 PTS submission and therefore were not considered in support of the marketing application.

1. Good functional outcome at 3 months (mRS 0-2 or no worsening from baseline if baseline mRS ≥3). This secondary endpoint was evaluated with the following non-inferiority hypothesis test:

$$H_0: P_{SOC+MMAE} - P_{SOC} \leq -12\%$$
$$H_1: P_{SOC+MMAE} - P_{SOC} > -12\%$$

where $P_{SOC+MMAE}$ and P_{SOC} are the proportions of success in subjects who reported good functional outcomes at 3 months in the treatment and control groups, respectively. This endpoint used a non-inferiority margin of 12%.

B. Accountability of PMA Cohort

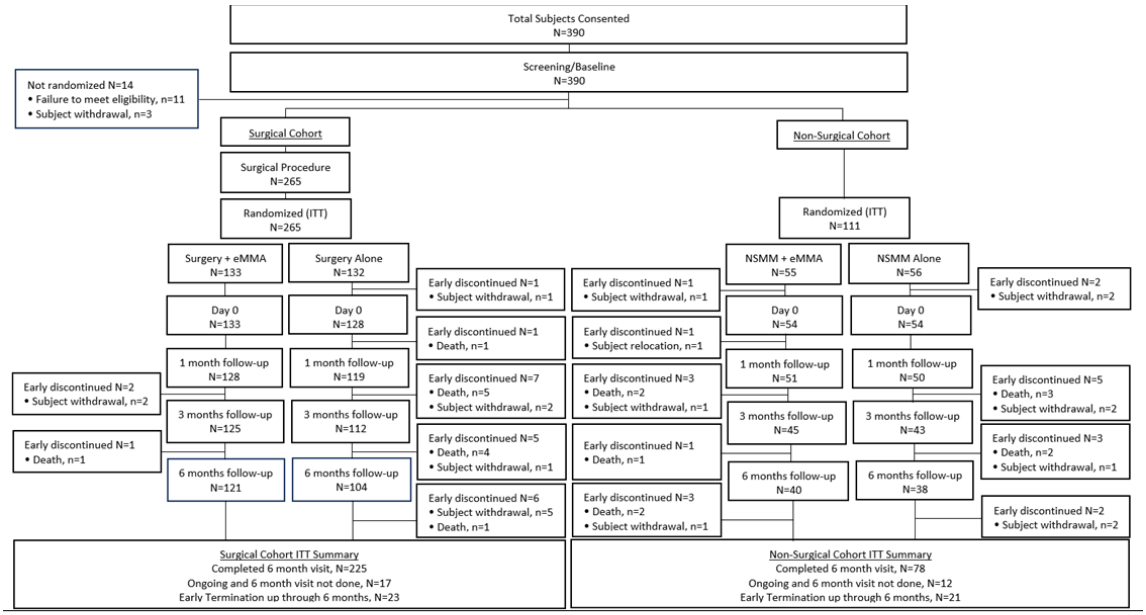
At the time of database lock, 390 patients enrolled in the MEMBRANE study of which 376 subjects were randomized including 188 test subjects (133 MMAE + surgery, 55 MMAE + NSMM) and 188 control subjects (132 surgery alone, 56 NSMM alone). Of subjects that were consented but not randomized, 11 failed to meet eligibility criteria and 1 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.

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 was 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). Subject accountability throughout the study is shown in Figure 2 and Table 1.



Source: Figure 3.1.1.3

eMMA = middle meningeal artery embolization; NSMM = non-surgical medical management.

Note: The reason is provided for all subjects who discontinued the study early. Subjects who did not discontinue early from the study (i.e., are ongoing) but missed a follow-up visit are not summarized.

Figure 2. Subject Accountability

Table 1. Study compliance at the 6-month primary endpoint visit (ITT Analysis Set)

	Surgical Cohort		NSMM Cohort	
Patient Accountability	**TRUFILL + Surgery**	**Surgery Alone**	**TRUFILL + NSMM**	**NSMM Alone**
Total Patients	133	132	55	56
Eligible n/N (%)				
6-month Follow up Visit Completed	121/133 (91.0)	104/132 (78.8)	40/55 (72.7)	38/56 (67.9)
Missed visit	9/133 (6.8)	8/132 (6.1)	6/55 (10.9)	6/56 (10.7)
Non-Eligible n/N (%)				
Did not receive assigned treatment	4/133 (3.0)	9/132 (6.8)	4/55 (7.3)	6/56 (7.1)
Death	1/133 (0.8)	11/132 (8.3)	5/55 (9.1)	5/56 (8.9)
Withdrawal	2/133 (1.5)	9/132 (6.8)	3/55 (5.5)	7/56 (12.5)
Subject relocated to another geographical location	0/133 (0.0)	0/132 (0.0)	1/55 (1.8)	0/56 (0.0)

Note: 4 subjects in the 'TRUFILL + Surgery' arm and, 4 subjects in the 'TRUFILL+ NSMM' arm did not receive TRUFILL LES,

Note: In the 'Surgery Alone' group 1 subject received the TRUFILL LES within 10 days of surgery, 2 subjects received TRUFILL LES after 10 days from surgery, 5 subjects received a non-TRUFILL LES and 1 subject withdrew prior to treatment. In the 'NSMM Alone' arm, 2 subjects received TRUFILL LES after 10 days from surgery, 2 subjects received a non-TRUFILL LES, and 2 subjects withdrew prior to treatment.

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

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a study evaluating treatment of SDH performed in the US. A listing of patient demographics and baseline characteristics are shown in Table 2. A listing of baseline SDH clinical characteristics are shown in Table 3. A listing of treatment and procedural details are shown in Table 4.

Table 2. Patient Demographics and Baseline Characteristics (ITT Analysis Set)

	Test Arm	Control Arm
Parameter	**TRUFILL + SOC**	**SOC Alone**
Age (years)		
Mean ± SD (N)	70.9 ± 10.64 (188)	70.3 ± 12.05 (188)
Median (Range)	73.0 (29 – 89)	73.0 (35 – 90)
Sex, n/N * (%)		
Male	143/188 (76.1)	139/188 (73.9)
Female	45/188 (23.9)	49/188 (26.1)
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 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)
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)
Hypertension, n/N * (%)	124/188 (66.0)	138/188 (73.4)
Current Smoker, n/N * (%)	22/188 (11.7)	18/188 (9.6)
Current 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)

Note: 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.

[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).

Table 3. Baseline SDH Clinical Characteristics (ITT Analysis Set)

	Test Arm	Control Arm
SDH Parameter	**TRUFILL + SOC**	**SOC Alone**
Anatomic side of SDH, n/N* (%)		
Bilateral	20/188 (10.6)	27/188 (14.4)
Unilateral	168/188 (89.4)	161/188 (85.6)
SDH Thickness, mm		
Mean ± SD (N)	15.19 ± 5.097 (187)	15.06 ± 5.110 (185)
Median (Range)	14.65 (4.0 – 29.5)	14.50 (4.1 – 31.5)
Presence of an acute component	160/187 (85.6)	157/185 (84.9)
Midline Shift (mm)		
Mean ± SD (n)	4.70 ± 3.311 (187)	4.51 ± 2.879 (185)
Median (Range)	4.87 (0.0 – 14.2)	4.57 (0.0 – 13.1)
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 ± SD (n)	1.0 ± 0.63 (187)	1.0 ± 0.65 (188)
Median (Range)	1.0 (0 – 2)	1.0 (0 – 2)
Baseline mRS		
Mean ± SD (n)	1.59 ± 1.038 (188)	1.55 ± 0.982 (188)
Median (Range)	1.5 (0 – 3)	1.0 (0 – 3)

Note: 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.

Table 4. Treatment and Procedural Details (ITT Analysis Set)

Parameter	TRUFILL + Surgery	TRUFILL + NSMM
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 ± SD (n)	71.1 ± 31.99 (129)	71.5 ± 33.65 (51)
Median (Range)	65.0 (21 – 154)	69.0 (20 – 187)
Surgical Procedure type, n/N* (%)		
Craniotomy	47/133 (35.3)	Not applicable
Burr-hole Evacuation	95/133 (71.4)	
Vascular access, n/N* (%)		
Radial artery	56/129 (43.4)	26/51 (51.0)
Femoral artery	73/129 (56.6)	25/51 (49.0)

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

D. Safety and Effectiveness Results

1. Safety Results

The primary safety endpoint was overall incidence of AEs through 6 months and was based on the AT analysis set patients available through the 6-month evaluation. Within the AT population, 424 AEs occurred in 131/181 (71.8%) subjects in the test arm and 392 AEs occurred in 129/190 (65.3%) subjects in the control arm.

The key safety outcomes for this study are presented below in Table 5 and Table 6. Table 5 presents the overall incidence of adverse events by seriousness, severity, and relation through 6 months 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 6 presents neurological deaths and neurological events of interest through 6 months. No neurologic deaths associated with the device or embolization procedure were observed. A listing of AEs occurring at >1% may be found in the device labeling. Overall, the use of the TRUFILL LES did not present any unknown risks that have not been previously described.

Table 5. Overall Incidence of AEs by Seriousness, Severity, and Relation through 6 months (ITT Analysis Set)

Relatedness	Test Arm TRUFILL + SOC[1] n/N (%)	Control Arm SOC[1] Alone n/N (%)
All AEs (including SAEs, non-SAEs) through 6 months	129/180 (71.7)	110/173 (63.6)
Non-SAEs	110/180 (61.1)	95/173 (54.9)
SAEs	50/180 (27.8)	49/173 (28.3)
SAEs Related to Embolization Procedures through 6 months	4/180 (2.2)	Not Applicable
SAEs Related to TRUFILL through 6 months[2]	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

[1]SOC is standard of care surgery or NSMM

[2]The single device related SAE was a cerebral artery infarct

Note: This data excludes 8 subjects in the test arm who did not receive the TRUFILL LES and 15 subjects that received a liquid embolic (TRUFILL or other) in the control arm (without any crossover)

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

Table 6. Neurologic Death and Neurologic Events of Interest through 6 Months (ITT Analysis Set)

	Test Arm	Control Arm
	TRUFILL + SOC[1]	**SOC[1] Alone**
Death Classification and Relatedness[2]	n/N (%) [# events]	n/N (%) [# events]
All Neurologic Deaths[2]	3/180 (1.7) [3]	4/173 (2.3) [4]
Related to Study Device[2]	0/180 (0.0) [0]	Not Applicable
Related to Embolization Procedure[2]	0/180 (0.0) [0]	Not Applicable
Related to Surgery Procedure[2,3]	0/129 (0.0) [0]	4/123 (3.0) [4]
Related to SDH Medication[2]	0/180 (0.0) [0]	0/173 (0.0) [0]
Other[4]	3/180 (1.7) [3]	0/173 (0.0) [0]
Neurologic Events of Interest[2]		
Stroke[2]	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[2]	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]

[1]SOC is standard of care surgery or NSMM
[2]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.
[3]Denominator is based on the number of patients receiving surgery.
[4]Other relatedness is defined as relatedness not pertaining to study device, embolization procedure, surgery procedure, or SDH medication.
Note: This data excludes 8 subjects in the test arm who did not receive the TRUFILL LES and 15 control subjects that did not received their treatment assignment (without any crossover).
Note: n = number of subjects with data available by category; N = number of subjects in the analysis set.

2. Effectiveness Results

The primary effectiveness analysis was based on the ITT population at the 6-month timepoint. Key effectiveness outcomes are presented in Table 7 and Table 8.

Primary Effectiveness Results

The primary 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 7, the primary analysis resulted in an odds ratio of 0.475 (90% CI: 0.239, 0.944) for the surgical cohort favoring the TRUFILL 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. 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 8 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 exclude patients that did not receive their treatment assignment, including control patients that received a liquid embolic. These trends were similar in the combined cohort.

The sponsor conducted a sensitivity analysis using the PP and AT populations. Importantly, the PP population 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 population 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 population, 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 7. Primary Effectiveness Endpoint (ITT population)

Category	Surgical Cohort		NSMM Cohort		Overall N=376
	TRUFILL + Surgery	Surgery Alone	TRUFILL + NSMM	NSMM Alone	
Primary effectiveness endpoint at 6 months with observed data, n/N* (%)	9/106 (8.5)	19/94 (20.2)	8/40 (20.0)	10/37 (27.0)	
Estimate of odds ratio with imputed data (90% CI)	0.475 (0.239, 0.944)	-	0.615 (0.266, 1.419)	-	
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 CMH test					0.044

CI = confidence interval; CMH = Cochran-Mantel-Haenszel;

Note: Odds ratio (OR) and common odds ratio are both 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.

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 any re-operation or surgical procedure on the SDH within 6 months post randomization.

Note: Subjects with missing data of the primary effectiveness endpoint were imputed using multiple imputation with diabetes, hypertension, location of SDH, MGS score (baseline, 1 month, and 3 months), mRS score (baseline and 3 months), MMSE score (baseline), hematoma ABC volume (1 month, 3 months, and 6 months), and hematoma thickness (1 month and 3 months), and 25 imputed datasets were generated, then combined for final estimate.

Note: n = number of subjects with data available by category; N = number of subjects in the analysis set and excludes subjects that did not receive their treatment assignment.

Note: Denominator (N*) for the percentage is based on the number of subjects with non-missing values of the primary effectiveness endpoint. This analysis includes 8 subjects in the test arm and 15 subjects in the control arm who did not receive their assigned treatment

Table 8. Primary Effectiveness Endpoint by Reason (ITT Population)

Category	Surgical Cohort		Combined Cohort	
	TRUFILL + Surgery	**Surgery Alone n/N* (%)**	**TRUFILL + SOC n/N* (%)**	**SOC Alone n/N* (%)**
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[+]				
Due to residual or re-accumulation of the cSDH (>10mm) per independent core lab at 6 months n/N (%)	6/104 (5.8)	3/86 (3.5)	10/143 (7.0)	6/119 (5)
Due to re-operation or surgical procedure on the SDH within 6 months n/N (%)	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 n/N (%)	0/104 (0.0)	0/86 (8.5)	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 n/N (%)	0/104 (0.0)	2/86 (2.3)	0/143 (0.0)	2/119 (1.7)

CEC = clinical events committee; SDH = subdural hematoma; 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: n = number of subjects with data available by category; N = number of subjects in the analysis set excluding subjects who did not receive their assigned treatment.

Note: Denominator (N*) for the percentage for the primary endpoint is based on the number of subjects with non-missing values of the primary effectiveness endpoint. This primary analysis includes 8 subjects in the test arm and 15 subjects in the control arm who did not receive their assigned treatment

[+]Test subjects who were randomized to receive TRUFILL but did not receive TRUFILL and control subjects who did not receive their treatment assignment were excluded from data reporting on event by reason

Hypothesis Driven Secondary Endpoints

The study prespecified three hierarchical hypothesis driven secondary endpoints. Only the first level of the hierarchy was available at the time of PMA submission which evaluates non-inferiority of the test group and control group for good functional outcome at 3 months defined as mRS 0-2 or no worsening from baseline if baseline mRS ≥3. As shown in Table 9, 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 9. Good Functional Outcome at 3 months

Category	Surgical Cohort		Combined Cohort	
	TRUFILL Surgery	**Surgery Alone**	**TRUFILL + SOC**	**SOC Alone**
Good functional outcome at 3 months (observed data), n/N (%)	95/105 (90.5)	76/97 (78.4)	122/143 (85.3)	104/135 (77.0)
Estimate for risk difference with imputed data (90% CI) – Combined Cohort	0.073 (-0.001, 0.147)			

CI = confidence interval; MMAE = middle meningeal artery embolization; NSMM = non-surgical medical management; mRS = modified Rankin Score; SOC = standard of care surgery or NSMM.
Note: A subject is considered to have a good functional outcome if the 3-month mRS is less than or equal to 2 or otherwise no worsening from baseline mRS if the baseline mRS is greater than or equal to 3.
Note: Subjects with missing mRS scores due to death prior to 3 months will be considered to have a score of 6 in the analysis. Subjects with missing data at 3 months due to reasons other than death will be imputed with multiple imputation.
Note: Missing mRS were imputed with age, mRS score (1 month), diabetes, ischemic stroke, and hypertension, and 25 imputed datasets were generated, then combined for a final estimate.
Note: n = number of subjects with data available by category; 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 + SOC" vs. "SOC Alone" arm.

Additional analyses

Post-hoc Effectiveness Endpoint

The sponsor conducted a post-hoc analysis 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 10 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 10. Post-hoc Composite Endpoint at 6 Months

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[+]				
Due to worsening in hematoma volume at 6 months compared to baseline n/N (%)	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 n/N (%)	5/104 (4.8)	10/85 (11.8)	9/143 (6.3)	12/122 (9.8)
Due to all-cause mortality through 6 months n/N (%)	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 n/N (%)	5/104 (4.8)	1/85 (1.2)	7/143 (4.9)	1/122 (0.8)

CEC = clinical events committee; SDH = subdural hematoma;
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: n = number of subjects with data available by category; N = number of subjects in the analysis set.
Note: Denominator (N*) for the percentage is based on the number of subjects with non-missing values of the primary effectiveness endpoint.
This post-hoc composite effectiveness endpoint analysis includes 8 subjects in the test arm and 15 subjects in the control arm who did not receive their assigned treatment.
[+]Test subjects who were randomized to receive TRUFILL but did not receive TRUFILL and control subjects who were randomized to receive SOC but received TRUFILL within 10 days of randomization were excluded from data reporting on event by reason.

The sponsor provided a Kaplan-Meier analysis of time to surgical procedure on SDH post-randomization. As shown in Figure 3, all post-randomization surgical procedures occurred within 44 days of randomization.

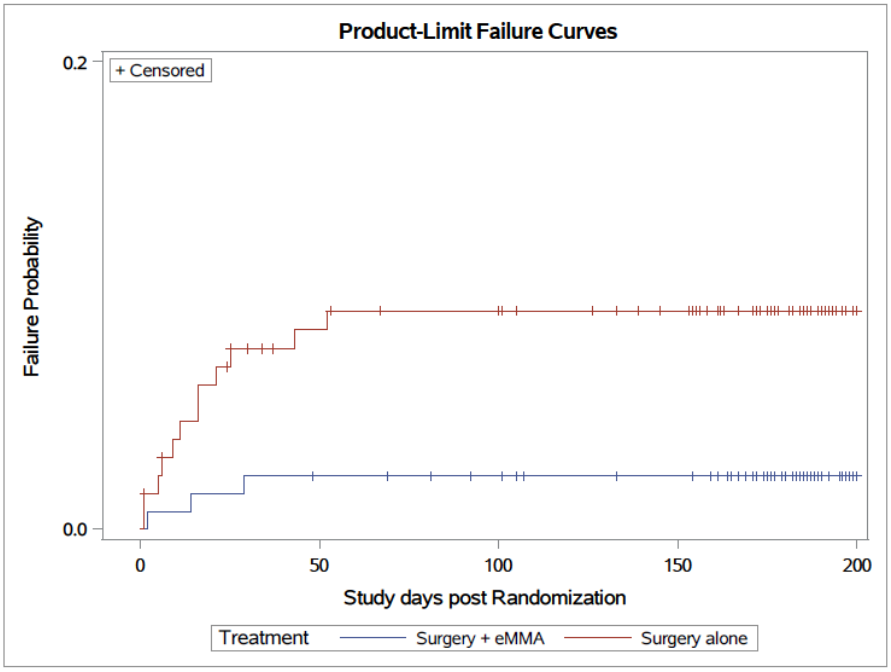


Figure 3. Kaplan-Meier Analysis of Time to Surgical Procedure on SDH Post-Randomization

3. Subgroup Analyses

The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes: ethnicity, race, age, sex and region and site homogeneity. Significant differences among subgroups were not identified as shown in Table 11, Table 12, and Table 13. These subgroup analyses were exploratory in nature and should be interpreted with caution, as the study was not specifically powered for subgroup comparisons.

Table 11. Subgroup Analyses of Primary Effectiveness Endpoint by Race, Ethnicity, and Age (ITT Set, N=376)

Primary effectiveness endpoint event	Surgical Cohort (N=265)			Non-Surgical Cohort (N=111)		
	Surgery + MMAE N=133 n/N* (%)	Surgery Alone N=132 n/N* (%)	OR (90% exact CI)	NSMM + MMAE N=55 n/N* (%)	NSMM Alone N=56 n/N* (%)	OR (90% exact CI)
Primary effectiveness endpoint at 6 months with observed data, n/N* (%)	9/106 (8.5)	19/94 (20.2)	0.366 (0.161, 0.802)	8/40 (20.0)	10/37 (27.0)	0.675 (0.240, 1.875)
Ethnicity						
Hispanic or Latino (n=26)	0/8 (0.0)	2/7 (28.6)	0.000 (0.000, 1.784)	0/2 (0.0)	1/1 (100.0)	0.000 (0.000, 4.500)
Not Hispanic or Latino (n=344)	9/97 (9.3)	17/84 (20.2)	0.403 (0.174, 0.904)	8/38 (21.1)	9/35 (25.7)	0.770 (0.267, 2.208)
Not reported (n=6)	0/1 (0.0)	0/3 (0.0)	-	-	0/1 (0.0)	-
Race						
American Indian or Alaskan Native (n=1)	-	0/1 (0.0)	-	-	-	-
Asian (n=35)	1/15 (6.7)	1/12 (8.3)	0.786 (0.019, 32.934)	0/3 (0.0)	0/1 (0.0)	-
Black or African American (n=55)	1/15 (6.7)	4/13 (30.8)	0.161 (0.006, 1.563)	0/6 (0.0)	2/5 (40.0)	0.000 (0.000, 1.646)
White (n=252)	6/67 (9.0)	12/61 (19.7)	0.402 (0.140, 1.081)	8/29 (27.6)	7/28 (25.0)	1.143 (0.361, 3.651)
Not Reported (n=31)	1/8 (12.5)	2/7 (28.6)	0.357 (0.011, 6.124)	0/2 (0.0)	1/3 (33.3)	0.000 (0.000, 13.500)
Other (n=2)	0/1 (0.0)	-	-	-	-	-
Age (years)						
< 75 years (n=217)	7/61 (11.5)	8/49 (16.3)	0.664 (0.227, 1.922)	4/23 (17.4)	6/18 (33.3)	0.421 (0.095, 1.799)
>= 75 years (n=159)	2/45 (4.4)	11/45 (24.4)	0.144 (0.022, 0.608)	4/17 (23.5)	4/19 (21.1)	1.154 (0.229, 5.776)

CI = confidence interval; SDH = subdural hematoma; MMAE = middle meningeal artery embolization; NSMM = non-surgical medical management;
Note: Odds ratio (OR) 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.
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 any re-operation or surgical procedure on the SDH within 6 months post randomization.
Note: Subjects with missing values are excluded from analysis.
Note: n = number of subjects with data available by category; N = number of subjects in the analysis set.
Note: Denominator (N*) is based on the number of subjects with non-missing values on the primary effectiveness endpoint.

Table 12. Subgroup Analysis of Primary Effectiveness Endpoint by Sex (ITT Set, N=376)

	Surgical Cohort (N=265)		Non-Surgical Cohort (N=111)		
Category	Surgery + MMAE N=133 n/N* (%)	Surgery Alone N=132 n/N* (%)	NSMM + MMAE N=55 n/N* (%)	NSMM Alone N=56 n/N* (%)	Overall N=376 p-value
Primary effectiveness endpoint at 6 months with observed data	9/106 (8.5)	19/94 (20.2)	8/40 (20.0)	10/37 (27.0)	0.288
Female (n=94)	1/26 (3.8)	8/26 (30.8)	2/9 (22.2)	2/10 (20.0)	
Male (n=282)	8/80 (10.0)	11/68 (16.2)	6/31 (19.4)	8/27 (29.6)	

SDH = subdural hematoma; MMAE = middle meningeal artery embolization; NSMM = non-surgical medical management;
Note: P-value for the interaction term is estimated from a logistic regression: primary effectiveness endpoint event (yes vs. no) = cohort + treatment + sex + sex*treatment. A non-significant p-value (>0.15) supports poolability across sex.
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 any re-operation or surgical procedure on the SDH within 6 months post randomization.
Note: Subjects with missing values are excluded from analysis.
Note: n = number of subjects with data available by category; N = number of subjects in the analysis set.
Note: Denominator (N*) is based on the number of subjects with non-missing values on the primary effectiveness endpoint by sex.

Table 13. Subgroup Analysis of Primary Effectiveness Endpoint by Region (ITT Set, N=376)

Category	Surgical Cohort (N=265)		Non-Surgical Cohort (N=111)		Overall N=376
	Surgery + MMAE N=133 n/N* (%)	Surgery Alone N=132 n/N* (%)	NSMM + MMAE N=55 n/N* (%)	NSMM Alone N=56 n/N* (%)	p-value
Primary effectiveness endpoint at 6 months with observed data	9/106 (8.5)	19/94 (20.2)	8/40 (20.0)	10/37 (27.0)	0.435
US (n=350)	8/94 (8.5)	19/84 (22.6)	8/39 (20.5)	10/36 (27.8)	
China (n=26)	1/12 (8.3)	0/10 (0.0)	0/1 (0.0)	0/1 (0.0)	

SDH = subdural hematoma; MMAE = middle meningeal artery embolization; NSMM = non-surgical medical management;

Note: P-value for the interaction term is estimated from a logistic regression: primary effectiveness endpoint event (yes vs. no) = region + cohort + treatment + region*treatment.

Note: Subjects with missing data of the primary effectiveness endpoint were imputed using multiple imputation with diabetes, hypertension, location of SDH, MGS score (baseline, 1 month, and 3 months), mRS score (baseline and 3 months), MMSE score (baseline), hematoma ABC volume (1 month, 3 months, and 6 months), and hematoma thickness (1 month and 3 months), and 25 imputed datasets were generated, then combined for final estimate.

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 any re-operation or surgical procedure on the SDH within 6 months post randomization.

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

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

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 149 investigators of which 0 were full-time or part-time employees of the sponsor and 16 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 16
- Proprietary interest in the product tested held by the investigator: 0

- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Neurological Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the MEMBRANE trial, as compared to the control group, patients receiving the TRUFILL LES overall demonstrated clinically meaningful improvement. The study met the primary effectiveness endpoint of residual or re-accumulation of the SDH (>10 mm) or re-operation or surgical procedure on the SDH within 6 months post-randomization with a common odds ratio of 0.529 (90% CI: 0.308, 0.909) with a one-sided p-value of 0.044. The study was not powered to assess the primary endpoint for the surgical alone; however, results trended favorably when considering subjects who received TRUFILL LES as an adjunct to surgery.

The study demonstrated non-inferiority of the TRUFILL LES to SOC for the secondary endpoint of good functional outcome (defined as mRS 0-2 or no worsening from baseline if baseline mRS ≥3) with 122/143 (85.3%) of test group subjects and 104/135 (77.0%) of control group subjects experiencing good functional outcomes at 3 months. These results demonstrate the benefit of TRUFILL LES as an adjunct to surgery for the treatment of subacute and acute SDH.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in the clinical study to support PMA approval as described above. 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 (a cerebral artery infarct) related to the device. In addition, 4/180 (2.2%) subjects experienced SAEs related to the embolization procedure. The most common device related AE was seizure. 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. Overall

the low rates and severity of adverse events observed in the MEMBRANE study demonstrate that MMAE with the TRUFILL LES as an adjunct to surgery is safe in the target patient population.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in the MEMBRANE clinical study conducted to support the PTS approval as described above. The probable benefits of the device include a reduced incidence of residual or re-accumulated SDH that requires surgical interventions, while avoiding poor clinical outcomes, clinical and functional deterioration.

The probable risks of the device are also based on data collected in the MEMBRANE clinical study conducted to support the PTS approval as described above. The probable risks of the device include seizures, non-target vessel embolization, vascular access site complications, arterial rupture thromboembolic complications, and other adverse events common to neurointerventional procedures.

Uncertainty in this study exists due to missing data for the primary endpoint, with an overall missing data rate of 26.3%. A tipping point analysis demonstrated that if 8 out of 54 missing treatment group subjects (approximately 15%) were considered failures without any additional successes in the control arms, the combine population outcome would lose statistical significance. In addition to data missing data, 8 ITT subjects in the test arm and 15 subjects in control arm did not receive their assigned treatments. The sponsor conducted a sensitivity analysis using the PP and AT populations. The analysis on the PP population excluded subjects that did not receive their assigned treatment and did not meet significance. This finding raises uncertainty regarding the robustness of the primary effectiveness result. However, the analysis on the AT population, which assessed patients based on the assigned treatment, reached significance. Importantly, the non-surgical cohort did not demonstrate statistical significance as a standalone dataset. While the MEMBRANE study was not powered to demonstrate significance, trends in a component-level post-hoc analysis did not provide assurance of benefit of the TRUFILL LES as a standalone treatment of SDH, which may be a result of small sample sizes in this cohort. While these findings indicate some uncertainty regarding the robustness of the treatment effect, the results from the surgical cohort and combined cohort along with the sensitivity analyses support the overall conclusion of treatment benefit for the combined population.

1. Patient Perspective
   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that the probable benefits of MMAE with the TRUFILL LES as an adjunct to surgery for symptomatic subacute and chronic subdural hematoma outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the TRUFILL LES when used in accordance with the indications for use. The MEMBRANE study demonstrated that MMAE with the TRUFILL LES as an adjunct to surgery for symptomatic subacute and chronic subdural hematoma confers substantial clinical benefit with minimal additional harm. The available results demonstrate that MMAE with TRUFILL LES as an adjunct to surgery is safe and effective for the treatment of symptomatic subacute and chronic subdural hematoma, and that the benefits are significant and outweigh the risks associated with the procedure.

XIV. CDRH DECISION

CDRH issued an approval order on December 16, 2025. The final clinical conditions of approval cited in the approval order are described below.

The purpose of the Post-Approval Study (PAS) is to characterize the safety and effectiveness of the TRUFILL n-Butyl cyanoacrylate (n-BCA) Liquid Embolic System during real-world use for middle meningeal artery (MMA) embolization in patients with symptomatic subacute and chronic subdural hematoma (SDH). This study will include prospective all-comers enrollment to include all subjects in whom the TRUFILL n-BCA Liquid Embolic System is used for MMA embolization in a single-arm trial with a minimum total enrollment of 250 subjects. The primary outcome will be the rate of hematoma recurrence/progression requiring surgical drainage within 180 days. Additional outcome measures will include neurologic death, change in modified Rankin Scale (mRS), change in hematoma thickness, and change in midline shift with respect to baseline (pre-embolization). All relevant adverse events (AEs) will be recorded and reported throughout the study.

The primary outcome will be compared to historical outcomes of surgical correction of SDH derived from literature and the surgery only subjects in the control arm of the MEMBRANE clinical trial. Procedural information including timing of embolization with respect to surgery, access challenges, delivery catheter entrapment, and device embolization into unintended vessels will be assessed descriptively. The all-comers study should also record all devices used to deliver the study device during the procedure, such as the access and delivery catheters, delivery syringe size, and any adjunctive device use with TRUFILL n-BCA Liquid Embolic System. Follow up will occur at baseline (pre-embolization procedure), 24-72 hours post-procedure (surgery + MMA embolization) or prior to hospital discharge, 30 days, 90 days, and 180 days. Radiographic imaging assessments will be performed at baseline (prior to any intervention with surgery or MMA embolization), within 24-72 hours post-procedure (MMA embolization) or prior to hospital discharge (whichever comes first), 90 days if performed by the site as usual clinical care, and 180 days to assess hematoma size, neurologic assessments, and a survey of adverse events.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.