SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

XII. GENERAL INFORMATION

Device Generic Name:	Neurovascular Liquid Embolic Agent
Device Trade Name:	Onyx Liquid Embolic System (LES)
Device Procode:	SGU
Applicant's Name and Address:	Micro Therapeutics, Inc. d/b/a ev3 Neurovascular (a wholly owned subsidiary of Medtronic Inc.) 9775 Toledo Way Irvine, CA 92618

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P030004/S035

Date of FDA Notice of Approval: December 8, 2025

The original PMA of the Onyx LES, P030004, was first approved on July 21, 2005, and was indicated for the presurgical embolization of brain arteriovenous malformations (bAVMs). 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/pdf3/P030004B.pdf

The current supplement was submitted to expand the indication for the Onyx LES to include embolization of the middle meningeal artery (MMA) as an adjunct to surgery in the treatment of symptomatic subacute or chronic subdural hematoma (SDH).

XIII. INDICATIONS FOR USE

1. Onyx Liquid Embolic System (LES) is indicated for presurgical embolization of brain arteriovenous malformation (bAVMs).

2. Onyx Liquid Embolic System (LES) is indicated for embolization of the middle meningeal artery (MMA) as an adjunct to surgery for the treatment of symptomatic subacute or chronic subdural hematoma (SDH).

XIV. CONTRAINDICATIONS

The use of the Onyx LES is contraindicated when any of the following conditions exist:

- When optimal catheter placement is not possible.
- When provocative testing indicates intolerance to the occlusion procedure.
- When vasospasm stops blood flow.

XV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Onyx LES labeling.

XVI. DEVICE DESCRIPTION

The Onyx LES device design is the same as approved under P030004. There are no design changes to the Onyx LES device for the proposed indication expansion. The description of the device is provided below for reference.

The Onyx LES is a non-adhesive liquid embolic agent comprised of ethylene vinyl alcohol (EVOH) copolymer dissolved in dimethyl sulfoxide (DMSO) and suspended micronized tantalum powder to provide contrast for visualization under fluoroscopy. The Onyx LES product consists of a 1.5 mL vial of the Onyx LES liquid embolic, a 1.5 mL vial of DMSO, two 1 mL Onyx LES delivery syringes, and one 1 mL DMSO delivery syringe (Figure 1). A delivery microcatheter compatible with Onyx LES and DMSO that is indicated for use in the neurovasculature is used to access the embolization site. An optional syringe adapter may be used if available for the associated microcatheter. The delivery microcatheter and syringe adapter are not provided with the Onyx LES. The Onyx LES is delivered through the microcatheter to the target location under fluoroscopic control. The DMSO solvent dissipates into the blood, causing the EVOH copolymer and suspended micronized tantalum to precipitate in situ and solidify.

Figure 1. Onyx LES

Onyx LES is available in two product formulations:

- Onyx LES 18: The Onyx LES 18 is comprised of 6% EVOH and has a nominal viscosity of 18 centistoke (cSt) at 40 °C.
- Onyx LES 34: The Onyx LES 34 is comprised of 8% EVOH and has a nominal viscosity of 33 cSt at 40 °C.

Due to the lower viscosity, Onyx LES 18 will travel more distally and penetrate deeper compared to the Onyx LES 34. Final solidification occurs within five minutes for both product formulations.

XVII. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of subacute or chronic subdural hematoma 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.

XVIII. MARKETING HISTORY

The Onyx LES is marketed for MMA embolization (MMAE) in SDH patients in the following international geographies: Australia, Austria, Belgium, Brazil, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Poland, Portugal, Republic of Ireland, Romania, Slovakia, Spain, Sweden, and United Kingdom. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

XIX. 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 complications such as fistula, pseudo-aneurysm, pain and tenderness, inflammation, necrosis, granuloma, pathological hand cold intolerance, amputation, hematoma or hemorrhage, compartment syndrome, hand dysfunction
- Allergic reaction
- Arrhythmia
- Catheter entrapment
- Catheter rupture
- Complications of radiation exposure (e.g., alopecia, burns ranging in severity from skin reddening to ulcers, cataracts, and delayed neoplasia) increases as the procedure time and the number of procedures increase
- Contrast related complications including but not limited to burning sensation, nausea, contrast nephropathy
- Death
- Device migration and cast movement
- Headache
- Infection
- Intracranial hemorrhage or hemorrhage in another vascular location
- Ischemic events: transient ischemic attack (TIA)/stroke

- Myocardial infarction
- Nerve damage or cranial nerve palsy
- Neurological deficits/dysfunctions
- Pulmonary embolism
- Seizures
- Thrombocytopenia
- Thromboembolic events
- Vascular complications including but not limited to dissection, perforation, rupture, occlusion, vasospasm, hypotension
- Visual complications related to anatomical variants (ophthalmic collateral)

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

XX. SUMMARY OF NON-CLINICAL STUDIES

A summary of previously reported non-clinical studies can be found in the SSED for the original PMA (P030004). No additional non-clinical studies were performed for the current application.

XXI. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of MMAE with Onyx LES as an adjunct to surgery for the treatment of symptomatic subacute or chronic SDH in the United States (U.S.) under investigational device exemption (IDE) # G190263. The study stratified enrollment by patients that were treated with surgery, with and without adjunctive embolization (surgical cohort), and those that were treated with medical management, with and without adjunctive embolization (observational cohort). Data from the surgical cohort of this clinical study were the basis for the PMA approval decision. A summary of the clinical study pertaining to the surgical cohort is presented below.

A. Study Design

In the surgical cohort, subjects were enrolled between December 3, 2020, and August 23, 2023. The database for this panel-track PMA supplement reflected data collected through February 23, 2024, and included 400 patients. There were 39 investigational sites in the U.S.

The study was a multi-center, prospective, randomized, interventional, controlled, open-label, adaptive design clinical study titled "Embolization of the Middle Meningeal Artery with Onyx Liquid Embolic System in the Treatment of Subacute and Chronic Subdural Hematoma (EMBOLISE)." Subjects who were allocated to the surgical cohort were then randomized to receive surgery and MMAE with Onyx LES (test group) or surgery only (control group). Patients were permitted to have surgery prior to or after

randomization into the test or control groups. Crossover was not permitted between the randomized arms.

The EMBOLISE study used an independent Data Monitoring Committee (DMC) and a Clinical Events Committee (CEC) to minimize bias, to assess the primary effectiveness and safety endpoints, as well as to oversee the safety of the study. A central independent Core Lab was also engaged in the study for uniform and independent evaluation of the imaging data.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the surgical cohort of the EMBOLISE study was limited to patients who met the following inclusion criteria:

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

   Patients were <u>not</u> permitted to enroll in the EMBOLISE study surgical cohort if they met any of the following exclusion criteria:

   1) Life expectancy is less than 1 year.
   2) Patient unable to be present or be available for follow-up.
   3) Female patient, of child-bearing potential, who is pregnant (confirmed with a positive pregnancy test) or breastfeeding at the time of admission or plans to become pregnant during their participation in the study.

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

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 14 days, 30 days, 90 days, and 180 days postoperatively. Additional assessments were performed at baseline (screening and randomization), at the time of the procedure or immediately before, within 30 hours postoperative, and at discharge. Preoperative and postoperative follow-up evaluations include physical and functional assessments, laboratory measurements, 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 Endpoint

The original primary endpoint of the EMBOLISE study was CEC-adjudicated hematoma recurrence/progression requiring surgical drainage within 90 days post-treatment. However, based on discussions with the FDA, the sponsor developed a primary composite endpoint to incorporate clinical outcomes. This endpoint was developed after the completion of enrollment in the surgical cohort and collection of

follow-up data, but prior to data analysis. The updated primary endpoint was a composite of the rate of hematoma recurrence/progression requiring surgical drainage within 90 days post-treatment, OR poor clinical outcome, OR clinical deterioration at 90 days post-treatment.

In this endpoint, specific criteria for recurrence were based on incidence of radiographic recurrence of hematoma AND presentation of new or worsening symptoms within 90 days. Any target hematoma requiring surgical drainage within 90 days post-treatment was considered a primary endpoint failure. Poor clinical outcome was defined as MGS score 2-4, MSS score 0-3, or Glasgow Coma Scale (GCS) score 3-12. Clinical deterioration was defined as ≥ 1 point worsening in MGS, GCS, or MSS at 90 days compared to baseline (except MSS 5 at baseline to MSS 4 at 90 days). A subject was considered a failure for the primary endpoint if they met any of the criteria defined in the primary endpoint.

The primary endpoint was evaluated as a superiority analysis of the test group compared to the control group as shown below.

$$H_0: P_T = P_C \text{ vs. } H_1: P_T \neq P_C$$

P_T is the primary composite endpoint incidence rate in the test group and P_C is the corresponding rate in the control group.

With regard to success/failure criteria, the study was considered a success if the primary composite endpoint was met using a 2-tailed Fisher's exact test. The primary composite endpoint incidence rate was expressed with the corresponding 95% exact Clopper-Pearson confidence interval for each randomized treatment group. If the probability value of the Fisher's exact test was < 0.05 and a lower proportion of subjects in the test group than in the control group satisfied any one of the primary composite endpoint criteria, the primary objective was met.

Safety Endpoint

The safety endpoints were assessed descriptively for the following assessments.

- Incidence of procedural (device-related) serious adverse events (AEs) up to 30 days.
- Incidence of procedural (procedure-related) serious AEs up to 30 days.
- Incidence of neurological death up to 90 days and 180 days.
- Incidence of device-related AEs up to 90 days and 180 days.

Clinical Secondary Hypothesis Driven Endpoint

The clinical secondary endpoint evaluated the non-inferiority of the test group compared to the control group, based on deterioration in neurologic function at 90 days (one-sided). Deterioration was defined as having an mRS score < 3 at baseline

and ≥ 3 at 90 days or having an mRS score ≥ 3 at baseline and having an increase of ≥ 1 mRS unit at 90 days. The clinical secondary endpoint was defined as follows:

$$H_0: P_T - P_C \geq 0.12 \text{ vs. } H_1: P_T - P_C < 0.12$$

P_T is the incidence of deterioration in the test group and P_C is the corresponding rate in the control group and a non-inferiority margin of 12% was used for the comparison. If the non-inferiority test of the endpoint was a success, a superiority test would be conducted.

B. Accountability of PMA Cohort

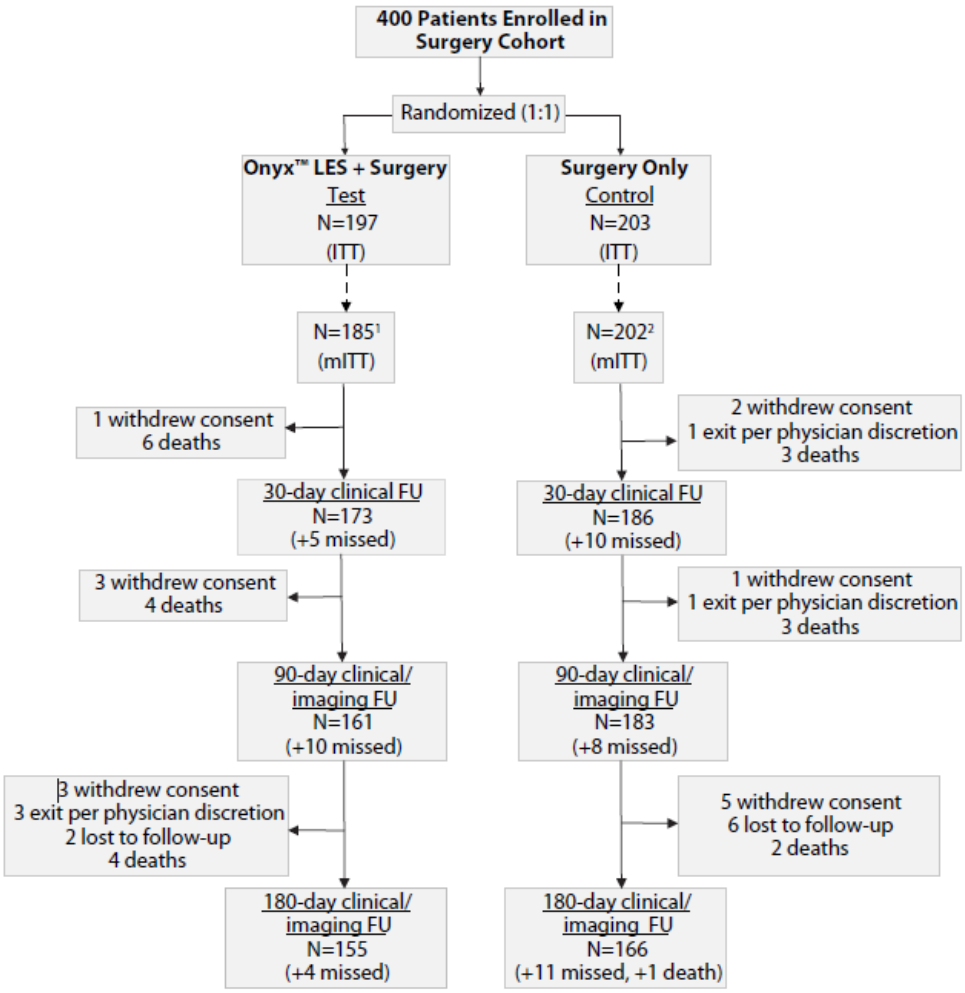
At the time of database lock, there were 400 patients enrolled in the EMBOLISE study including 197 test subjects and 203 control subjects. The following analysis populations were defined and used in the protocol:

Intention-to-Treat (ITT): This set includes all randomized subjects who signed the ICF and were randomized. The ITT population was used as the primary analysis set and included 197 test subjects and 203 control subjects.

Modified Intention-to-Treat (mITT): This set includes subjects in the ITT population excluding those who did not successfully complete the treatment procedure as assigned (185 test subjects and 202 control subjects). This data set was also used to evaluate the primary effectiveness endpoint, in addition to the ITT population, to evaluate the robustness of the study results in those patients who received the assigned intervention. The mITT data set was also used to analyze the secondary outcomes related to procedural success. One test subject withdrew consent prior to the procedure and 11 did not receive MMAE due to prohibitive anatomical variants. One control subject did not receive surgery.

Per Protocol (PP): This set includes subjects in the mITT population excluding those with deviations from the inclusion/exclusion criteria. This data set was used for sensitivity analyses.

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



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

Figure 2. Subject Accountability

Table 1. Study Compliance (mITT Population) at the 90-Day Primary Endpoint Visit

Patient Accountability	Test Arm	Control Arm
	Onxy LES + Surgery	Surgery Alone
Total mITT Patients[1]	**185**	**202**
Eligible	**171**	**191**
90-day Follow-up Visit Completed	161	183
Missed Visit	10	8
Non-Eligible	**14**	**11**
Death	10	6
Withdrawal	4	3
Lost to Follow-up	0	0
Other Reason[2]	0	2
Visit Not Yet Due	0	0

[1]Total mITT patients excludes patients who did not receive the treatment to which they were assigned including 11 test patients who did not receive the Onyx LES, one control patient who did not receive surgery, and 1 test patient who withdrew consent prior to treatment.
[2]Two patients in the control arm exited early per physician discretion.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a study evaluating treatment of symptomatic subacute and chronic SDH patients in the U.S. 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

	Test Arm	Control Arm
Parameter	**Onxy LES + Surgery (N=197)**	**Surgery Alone (N=203)**
Age (Years)		
Mean ± Standard Deviation (SD) (N)	73.0 ± 11.0 (197)	71.0 ± 11.3 (203)
Median (Range)	74.7 (21.7, 90.8)	72.5 (28.2, 90.2)
Sex		
Male	72.6% (143/197)	73.4% (149/203)
Female	27.4% (54/197)	26.6% (54/203)
Race		
Native American	0.0% (0/197)	0.5% (1/203)
Asian	3.0% (6/197)	3.9% (8/203)
Black or African American	10.7% (21/197)	11.3% (23/203)
Native Hawaiian or Pacific Islander	0.0% (0/197)	0.5% (1/203)
White	79.7% (157/197)	76.8% (156/203)
Unknown	6.6% (13/197)	6.9% (14/203)
Ethnicity		
Hispanic or Latino	9.6% (19/197)	13.3% (27/203)
Not Hispanic or Latino	90.4% (178/197)	85.7% (174/203)
Unknown	0.0% (0/197)	1.0% (2/203)
Current Smoker	9.6% (19/197)	12.8% (26/203)
Alcoholism	10.2% (20/197)	13.3% (27/203)
Prior Stroke	1.0% (2/197)	0.5% (1/203)
Antiplatelet and/or Anticoagulant Medication at Symptom Onset		
Antiplatelet Medication Only	28.4% (56/197)	28.1% (57/203)
Anticoagulant Medication Only	7.6% (15/197)	6.4% (13/203)
Antiplatelet and Anticoagulant Medication	2.0% (4/197)	4.4% (9/203)

Table 3. Baseline SDH Clinical Characteristics and Symptoms

	Test Arm	Control Arm
SDH Parameter	**Onyx LES + Surgery (N=197)**	**Surgery Alone (N= 203)**
Anatomic Side of SDH		
Bilateral	21.3% (42/197)	18.2% (37/203)
Unilateral	78.7% (155/197)	81.8% (166/203)
SDH Thickness (mm)		
Mean ± SD (N)	21.6 ± 6.3 (197)	21.4 ± 6.2 (203)
Median (Range)	21.0 (7.0, 39.0)	22.0 (7.0, 36.0)
SDH Morphology[1]		
Calcified	0.0% (0/197)	1.0% (2/203)
Homogenous	44.2% (87/197)	43.8% (89/203)
Layering	48.2% (95/197)	48.3% (98/203)
Septated	46.2% (91/197)	49.3% (100/203)
None of the Above	0.5% (1/197)	3.0% (6/203)
Cannot Determine	0.5% (1/197)	0.0% (0/203)
Midline Shift (mm)		
Mean ± SD (N)	7.9 ± 3.6 (197)	8.6 ± 4.1 (203)
Median (Range)	8.0 (0.0, 19.0)	8.0 (0.0, 26.0)
Hypertension	73.1% (144/197)	71.4% (145/203)
Headache	68.5% (135/197)	71.9% (146/203)
Cognitive Impairment	45.2% (89/197)	45.3% (92/203)
Speech Disturbance	28.9% (57/197)	31.5% (64/203)
Gait Impairment / Instability	71.1% (140/197)	67.5% (137/203)
Limb Weakness	58.4% (115/197)	57.6% (117/203)
Neurological Deficit	34.5% (68/197)	42.4% (86/203)
Baseline mRS		
Mean ± SD (N)	2.2 ± 1.12 (197)	2.3 ± 1.12 (203)
Median (Range)	2 (1, 5)	2 (1, 5)

[1]Presented data represents core-lab adjudicated data. Site-reported characteristics can be found in the device labeling.

Table 4. Treatment and Procedural Details

	Test Arm
Parameter	**Onyx LES + Surgery (N=197)[1]**
Side Treated	
Left	49.7% (92/185)
Right	46.5% (86/185)
Bilateral	3.8% (7/185)
MMAE Procedural Time (minutes) (N)	63.9 ± 30.86 (196)
Surgical Procedure Type	
Craniotomy	46.4% (91/196)
Burr-hole Evacuation	53.6% (105/196)
Device Model	
Onyx 18	95.1% (176/185)
Onyx 34	3.8% (7/185)
Onyx 18 & 34	1.1% (2/185)
Vascular Access	
Radial Artery	39.8% (78/196)
Femoral Artery	60.2% (118/196)

[1]The Onyx LES treatment summaries do not include eleven subjects who did not receive the embolization procedure.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the mITT cohort. The key safety outcomes for this study are presented below in Table 5 to Table 7. No device-related AEs were observed through 180 days of the index procedure. The rate of serious adverse events (SAEs) related to the embolization procedure alone was 2.2% (4/185) and included 1 event each of arterial rupture, ischemic stroke, cerebellar infarction, and a device malfunction (guide catheter breakage). The rate of SAEs isolated to the embolization procedure was observed to be lower than the rates associated with the surgical procedure. Within the mITT population, all-cause mortality observed throughout the study was higher in the test group compared to the control group, 7.6% (14/185) vs. 4.0% (8/202). The incidence of neurologic death was 4.9% (9/185) vs. 2.0% (4/202) for the test group and control group, respectively, at 90 days, and 5.9% (11/185) vs. 3.0% (6/202) for the test group and control group, respectively, at 180 days. In the test group, a total of 10/185 deaths were related to the SDH disease and 1/185 was related to the surgery procedure; none (0%) were related to the Onyx LES device or the MMA embolization procedure per the CEC review. In the control group, a total of 3/202 deaths were related to the SDH disease, and 3/202 deaths were related to the surgery procedure. Unintended vessel occlusion was observed in 0.5% (1/185) subjects in the test group. No events related to device migration or catheter entrapment occurred in the test group.

Table 7 presents key CEC-adjudicated neurological deaths and events of interest through end of study follow-up. The rates of stroke, cerebral infarction, seizures, and TIA between the test and control groups were similar. No subjects in the test group exhibited any ipsilateral visual symptoms, Onyx LES migration, or catheter entrapment. A full listing of adverse events may be found in the device labeling. Overall, the use of Onyx LES did not present any unknown risks that have not been previously described.

Table 5. CEC Adjudicated Surgery Procedure, Embolization Procedure, and Device-Related Adverse Events (mITT population)

Relatedness	Test Arm Onyx LES + Surgery (N=185)	Control Arm Surgery Alone (N=202)
SAEs Related to Surgery and Embolization Procedures[1] through 30 Days	10.8% (20/185) [24]	Not Applicable
SAEs Related to Embolization Procedure Only[2] through 30 Days	2.2% (4/185) [4]	Not Applicable
SAEs Related to Device[1] through 30 Days	0.0% (0/185) [0]	Not Applicable
AEs Related to Device through 90 Days	0.0% (0/185) [0]	Not Applicable
AEs Related to Device through 180 Days	0.0% (0/185) [0]	Not Applicable
Unintended Vessel Occlusion	0.5% (1/185) [0]	Not Applicable
Catheter Entrapment	0.0% (0/185) [0]	Not Applicable
Access Site Complications	1.6% (3/185) [0]	Not Applicable
Onyx LES Migration	0.0% (0/185) [0]	Not Applicable

Events are classified as 'Related' if the CEC reported the relationship as 'Causal Relationship' or 'Possible.'
[1]Includes surgery procedure-related events that are also related to the embolization procedure, as well as surgery procedure-related events that are also related to both the embolization procedure and the disease under study.
[2]For subjects in the test group, the surgical drainage procedure and the embolization procedure may have occurred on different days. Summaries include SAEs occurring from the day of the first procedure through 30 days after the last procedure.

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

Table 6. CEC Adjudicated Neurological Deaths Through 90 Days (mITT Population)

Death Classification and Relatedness[1]	Test Arm Onyx LES + Surgery	Control Arm Surgery Alone
Neurologic Deaths by Relatedness	4.9% (9/185)	2.0% (4/202)
Related to Study Device	0.0% (0/185)	Not Applicable
Related to Embolization Procedure[2]	0.0% (0/185)	Not Applicable
Related to Surgery Procedure[3]	0.5% (1/185)	1.0% (2/202)
Related to SDH Only	4.3% (8/185)	1.0% (2/202)
Subdural disease (index SDH) was stable or improved at the last follow-up visit[4]	3.2% (6/185)	1.0% (2/202)
Subdural disease (index SDH) worsened > 10% at the last follow-up visit[5]	0.5% (1/185)	0.5% (1/202)

Death Classification and Relatedness[1]	Test Arm Onyx LES + Surgery	Control Arm Surgery Alone
Indeterminate[6]	1.1% (2/185)	0.5% (1/202)

Days to death calculated from the date of randomization.
[1]Includes deaths indicated by the CEC as 'causal relationship' or 'possible' in each category.
[2]Includes embolization procedure-related events that are also related to the surgery procedure, as well as embolization procedure-related events that are also related to both the surgery procedure and the disease under study.
[3]Includes events related to the surgery procedure only, as well as surgery procedure-related events that are also related to the disease under study.
[4]The change in Core Lab-assessed mean SDH thickness comparing the last follow-up visit image to the time 0 (24-hour post-treatment) image was ≤ 10%.
[5]The change in Core Lab-assessed mean SDH thickness comparing the last follow-up visit image to the time 0 (24-hour post-treatment) image was > 10%.
[6]No available follow-up image after time 0.

Categorical measures: % (n/Total N)

Table 7. CEC Adjudicated Neurological Deaths and Events of Interest through 180 Days (mITT Population)

	Test Arm Onyx LES + Surgery	Control Arm Surgery Alone
Death Classification and Relatedness[1]		
Neurologic Deaths by Relatedness	5.9% (11/185)	3.0% (6/202)
Related to Study Device	0.0% (0/185)	Not Applicable
Related to Embolization Procedure[2]	0.0% (0/185)	Not Applicable
Related to Surgery Procedure[3]	0.5% (1/185)	1.5% (3/202)
Related to SDH Only	5.4% (10/185)	1.5% (3/202)
Subdural disease (index SDH) was stable or improved at the last follow-up visit[4]	4.3% (8/185)	1.5% (3/202)
Subdural disease (index SDH) worsened > 10% at the last follow-up visit[5]	0.5% (1/185)	1.0% (2/202)

	Test Arm	Control Arm
	Onyx LES + Surgery	**Surgery Alone**
Indeterminate[6]	1.1% (2/185)	0.5% (1/202)
Neurological Events of Interest		
Stroke[7]	0.5% (1/185) [1]	1.0% (2/202) [2]
Cerebral Infarction	2.2% (4/185) [4]	0.5% (1/202) [1]
Serious Intracranial Hemorrhage	0.0% (0/185) [0]	0.0% (0/202) [0]
Seizures	9.2% (17/185) [18]	8.4% (17/202) [17]
TIA	0.0% (0/185) [0]	0.0% (0/202) [0]
Ipsilateral Visual Symptoms	0.0% (0/185) [0]	Not applicable

[1]Includes deaths indicated by the CEC as 'causal relationship' or 'possible' in each category.
[2]Includes embolization procedure-related events that are also related to the surgery procedure, as well as embolization procedure-related events that are also related to both the surgery procedure and the disease under study.
[3]Includes events related to the surgery procedure only, as well as surgery procedure-related events that are also related to the disease under study.
[4]The change in Core Lab-assessed mean SDH thickness comparing the last follow-up visit image to the time 0 (24-hour post-treatment) image was ≤ 10%.
[5]The change in Core Lab-assessed mean SDH thickness comparing the last follow-up visit image to the time 0 (24-hour post-treatment) image was > 10%.
[6]No available follow-up image after time 0.
[7]Presented data represents mITT population. Stroke rates for the ITT population can be found in the Patient Brochure.

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

2. Effectiveness Results

The primary effectiveness analysis was based on the ITT population at the 90-day time point. Key effectiveness outcomes are presented in Table 8, Table 9, and Table 10.

Primary Effectiveness Results

The primary endpoint was a composite of the rate of hematoma recurrence/progression requiring surgical drainage within 90 days post-treatment, OR poor clinical outcome, OR clinical deterioration at 90 days post-treatment as defined in Section X.A. above.

One hundred and sixty-one (161) test group patients and 183 control group patients had data available at the 90-day primary endpoint. Multiple imputation was used to impute missing data for subjects who failed to attend the 90-day evaluation visit (e.g., due to early withdrawal from the study, loss-to-follow-up, or death). In the ITT population, the rate of the primary composite endpoint was significantly lower in the test group compared to the control group (8.6% vs. 15.8%, respectively, p=0.0330), thus the endpoint was met (Table 8).

Imputation methods used a missing at random (MAR) assumption which was justified through a patient-level assessment of observed adverse events and outcomes. A correlation between missingness and the primary endpoint outcomes were not observed.

Table 8. Results of the Primary Endpoint[1]

	ITT		mITT	
CEC-Adjudicated Primary Endpoint	**Onyx LES + Surgery (n=197)**	**Surgery Alone (n=203)**	**Onyx LES + Surgery (n=185)**	**Surgery Alone (n=202)**
Incidence[2] [95% Confidence Interval (CI)]	8.6% [5.1%, 13.5%]	15.8% [11.0%, 21.5%]	7.6% [4.2%, 12.4%]	15.8% [11.1%, 21.6%]
Relative Risk [95% CI]	0.55 [0.30, 0.98]		0.48 [0.25, 0.90]	
Fisher's Exact Test P-value	0.0330		0.0123	

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

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

Table 9. Hematoma Recurrence/Progression Requiring Surgical Drainage Within 90 Days

	ITT		mITT	
CEC-Adjudicated Hematoma Recurrence/ Progression Requiring Surgical Drainage within 90 Days Post-Treatment	**Onyx LES + Surgery (n=197)**	**Surgery Alone (n=203)**	**Onyx + Surgery (n=185)**	**Surgery Alone (n=202)**
I. Incidence[1,2] I. [95% CI]	4.1% [1.8%, 7.8%]	11.3% [7.3%, 16.5%]	3.2% [1.2%, 6.9%]	11.4% [7.4%, 16.6%]
Relative Risk [95% CI]	0.36 [0.11, 0.80]		0.28 [0.08, 0.68]	

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

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

Clinical Secondary Endpoint

The incidence of deterioration in neurologic function at 90 days was observed to be 11.9% in the test group and 9.8% in the control group, which demonstrated non-inferiority of the test group to the control group (Table 10). Because non-inferiority was met, a pre-specified superiority test was conducted which failed to meet superiority (p=0.79).

Table 10. Clinical Secondary Endpoint Results (ITT Population[1])

	Onyx LES + Surgery (n=197)	**Surgery Alone (n=203)**	Risk Difference [95% CI]	Non-inferiority P-value[3]
Incidence of Deterioration in Neurologic Function, % (n/N) [95% CI][2]	11.9% (21/177) [7.5%, 17.6%]	9.8% (18/184) [5.9%, 15.0%]	2.08% [-4.76%, 8.92%]	0.0022

[1]Analysis performed for the ITT population. Please see device label for analysis in the mITT population.
[2]Deterioration is defined as having mRS < 3 at baseline and ≥ 3 at 90 days or having mRS ≥ 3 at baseline and having an increase of ≥ 1 point at 90 days. mRS score of 6 (death) is imputed for patients who died before the 90-day assessment.
[3]P-value for the non-inferiority test. If the upper 95% confidence limit of the difference is < 0.12, the null hypothesis is rejected, and the Farrington-Manning test indicates strong evidence of non-inferiority.

Additional Analyses

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

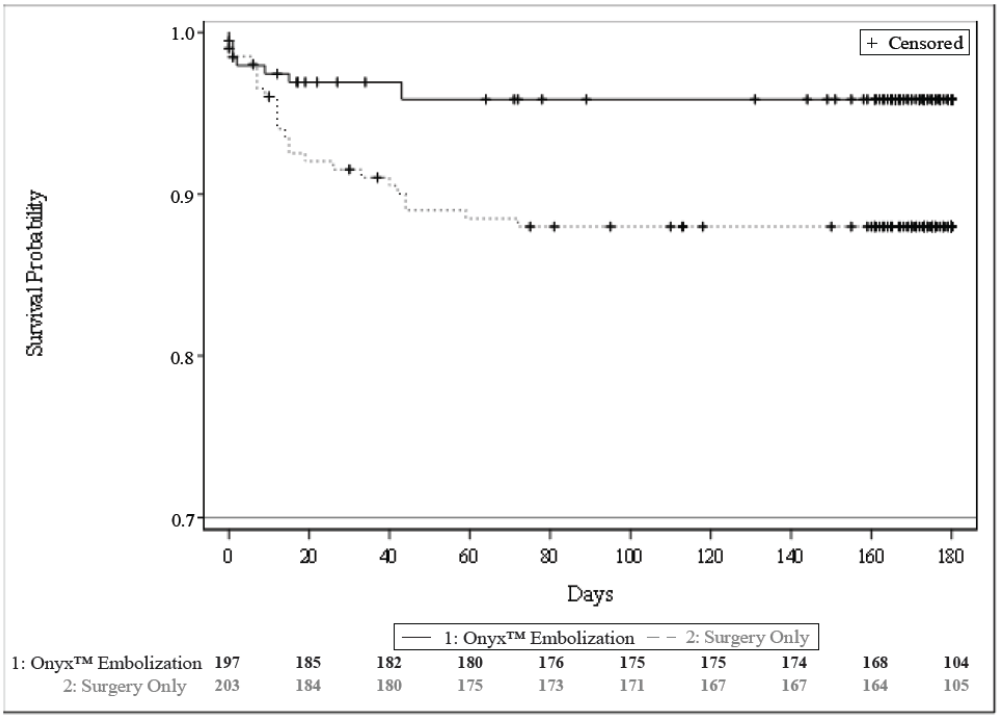


Figure 3. Kaplan-Meier Curve of Freedom from Re-Intervention Through Study Follow-Up

3. Subgroup Analyses

The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes: age, sex, race, ethnicity, disease state, timing of randomization, factors reported at randomization (hematoma thickness, MGS score, surgery type, antiplatelet and/or anticoagulant usage), and use/timing of antiplatelet/anticoagulant medication during the study. There was no significant difference in the treatment effect between the strata for subgroups as shown in Table 11. Caution should be taken when interpreting these results as the study was not specifically powered for the subgroups.

Table 11. Subgroup Analyses for the Primary Composite Endpoint[1] (ITT Population)

Variable	Heterogeneity of Treatment Effect[2]	Subgroup Stratum	Test Arm	Control Arm
			Onyx LES + Surgery[3,4] (N=197)	Surgery Alone[3,4] (N=203)
Median Age[5]	0.0525	≥ Median Age	8.0% (7/87) [3.3%, 15.9%]	25.3% (21/83) [16.4%, 36.0%]
		< Median Age	7.8% (6/77) [2.9%, 16.2%]	7.4% (7/95) [3.0%, 14.6%]
Age 65	0.8809	≥ 65 yrs	8.8% (12/136) [4.6%, 14.9%]	17.9% (24/134) [11.8%, 25.5%]
		< 65 yrs	3.6% (1/28) [0.1%, 18.4%]	9.1% (4/44) [2.5%, 21.7%]

Variable	Heterogeneity of Treatment Effect[2]	Subgroup Stratum	Test Arm	Control Arm
			Onyx LES + Surgery[3,4] (N=197)	Surgery Alone[3,4] (N=203)
Sex	0.3941	Male	7.8% (9/116) [3.6%, 14.2%]	17.7% (23/130) [11.6%, 25.4%]
		Female	8.3% (4/48) [2.3%, 20.0%]	10.4% (5/48) [3.5%, 22.7%]
Race	N/A	American Indian or Alaska Native	N/A	100.0% (1/1) [2.5%, 100.0%]
		Asian	0.0% (0/5) [0.0%, 52.2%]	14.3% (1/7) [0.4%, 57.9%]
		Black or African American	22.2% (4/18) [6.4%, 47.6%]	10.5% (2/19) [1.3%, 33.1%]
		Native Hawaiian or Other Pacific Islander	N/A	0.0% (0/1) [0.0%, 97.5%]
		White	6.9% (9/130) [3.2%, 12.7%]	16.9% (23/136) [11.0%, 24.3%]
		Not Otherwise Specified	0.0% (0/9) [0.0%, 33.6%]	9.1% (1/11) [0.2%, 41.3%]
		Not reported	0.0% (0/2) [0.0%, 84.2%]	0.0% (0/3) [0.0%, 70.8%]
Ethnicity	0.2750	Hispanic or Latino	14.3% (2/14) [1.8%, 42.8%]	12.0% (3/25) [2.6%, 31.2%]
		Not Hispanic or Latino	7.3% (11/150) [3.7%, 12.7%]	16.6% (25/151) [11.0%, 23.5%]
Disease State	0.4528	Subacute SDH	7.4% (5/68) [2.4%, 16.3%]	18.9% (14/74) [10.8%, 29.7%]
		Chronic SDH	8.3% (8/96) [3.7%, 15.8%]	13.5% (14/104) [7.6%, 21.6%]
Timing of Randomization	0.8195	Before Surgical Drainage	9.1% (11/121) [4.6%, 15.7%]	18.2% (20/110) [11.5%, 26.7%]
		After Surgical Drainage	4.7% (2/43) [0.6%, 15.8%]	11.8% (8/68) [5.2%, 21.9%]
Hematoma Thickness[6]	0.6763	0 mm to ≤ 15 mm	5.6% (2/36) [0.7%, 18.7%]	8.1% (3/37) [1.7%, 21.9%]
		> 15 mm	8.6% (11/128) [4.4%, 14.9%]	17.7% (25/141) [11.8%, 25.1%]
MGS Score[6]	0.6405	1	7.1% (8/112) [3.1%, 13.6%]	12.4% (14/113) [6.9%, 19.9%]
		2	9.6% (5/52) [3.2%, 21.0%]	21.5% (14/65) [12.3%, 33.5%]
Surgery Type[6]	0.3081	Burr Hole	5.8% (5/86) [1.9%, 13.1%]	16.5% (15/91) [9.5%, 25.7%]
		Craniotomy	10.3% (8/78) [4.5%, 19.2%]	14.9% (13/87) [8.2%, 24.2%]
Antiplatelet and/or Anticoagulant Usage[6] (Reported at Randomization)	0.9004	Yes	11.1% (4/36) [3.1%, 26.1%]	20.0% (9/45) [9.6%, 34.6%]
		No	7.0% (9/128) [3.3%, 12.9%]	14.3% (19/133) [8.8%, 21.4%]
Use of Antiplatelet and/or	0.7040	Yes	10.4% (8/77) [4.6%, 19.5%]	18.2% (16/88) [10.8%, 27.8%]

Variable	Heterogeneity of Treatment Effect[2]	Subgroup Stratum	Test Arm Onyx LES + Surgery[3,4] (N=197)	Control Arm Surgery Alone[3,4] (N=203)
Anticoagulant Medication Prior to Surgical Drainage Procedure or Through Study Follow-up		No	5.7% (5/87) [1.9%, 12.9%]	13.3% (12/90) [7.1%, 22.1%]
Timing of Antiplatelet and/or Anticoagulant Medication Usage During Follow-up	0.7912	Therapy Started within 7 Days Post-surgical Drainage Procedure[7]	6.3% (1/16) [0.2%, 30.2%]	18.8% (3/16) [4.1%, 45.7%]
		Therapy Started 8-30 Days Post-surgical Drainage Procedure	14.3% (2/14) [1.8%, 42.8%]	16.7% (3/18) [3.6%, 41.4%]
		Therapy Started ≥ 31 Days Post-surgical Drainage Procedure	9.1% (1/11) [0.2%, 41.3%]	16.7% (2/12) [2.1%, 48.4%]

All statistical tests and p-values for subgroups are considered exploratory, as tests for individual subgroups may not be sufficiently powered, and no multiple testing adjustment is applied.

[1]Hematoma recurrence/progression requiring surgical drainage within 90 days post-treatment OR clinical deterioration at 90 days post-treatment. Clinical deterioration is defined as ≥ 1 point worsening in MGS or GCS or MSS at 90 days compared to baseline (except MSS 5 at baseline → MSS 4 at 90 days).

[2]The Breslow-Day test is used to evaluate heterogeneity of the association between treatment and primary composite endpoint across each set of strata (heterogeneity of odds ratios).

[3]Denominator excludes subjects who failed to complete the 90-day evaluation visit (based on completion of 90-day imaging and completion of 90-day clinical assessments of Markwalder Grading Scale, Motor Strength Scale, and Glasgow Coma Scale) and who did not meet the CEC charter definition for primary endpoint failure before or at the 90-day visit.

[4]A 95% exact binomial Clopper-Pearson confidence interval is calculated for the incidence rate of the primary composite endpoint within each stratum.

[5]The median age among subjects in the ITT population: 73.5 years. Odds ratio for ≥ median age = 0.26 [0.09, 0.69]. Odds ratio for < median age = 1.06 [0.28, 3.88].

[6]As documented by the site in the interactive response technology system at the time of randomization.

[7]Also includes subjects who were on the medication at the time of surgical drainage and continued usage post-surgery.

Categorical measures: % (n/N)

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 182 investigators of which none were a full-time or part-time employee 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: 14
- Proprietary interest in the product tested held by the investigator: 2
- 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 Medtronic 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 EMBOLISE clinical study, as compared to the control group, patients receiving the Onyx LES in the ITT analysis population overall demonstrated clinically meaningful improvement when considering the primary composite endpoint of incidence of hematoma recurrence/progression requiring surgical drainage, poor clinical outcome, or clinical deterioration (8.6% vs. 15.8%, respectively, p=0.0330). The primary endpoint outcome was primarily driven by the rate of hematoma recurrence/progression requiring surgical drainage within 90 days post-treatment which favored the treatment arm. Additionally, the Onyx LES was found to be non-inferior to the control for the secondary clinical endpoint of neurologic function deterioration at 90 days. Together these findings demonstrate the benefit of the Onyx LES as an adjunct to surgery to reduce hematoma recurrence/progression in subacute and chronic SDH patients, while also avoiding overall poor clinical outcomes, deterioration in clinical status, or deterioration of neurologic function compared to surgery alone.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and/or animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The test group demonstrated a 2.2% (4/185) rate of SAEs related to the embolization procedure alone, with no (0%) observed device-related AEs through 180-day follow-up. Additionally, there were no (0%) events of ipsilateral visual symptoms, Onyx LES migration, or catheter entrapment, with 1 case (0.5%) of unintended embolization. The observed difference in the test and control arms in all-cause mortality and neurologic death were determined to be unrelated to the device per the CEC review and primarily related to progression of the SDH. Hence the EMBOLISE study demonstrated that MMA

embolization with Onyx LES as an adjunct to surgery is safe in the target patient population.

C. Benefit-Risk Determination

The probable benefits of the device include reduced incidence of hematoma recurrence/progression requiring additional surgical drainage while avoiding poor clinical outcomes or clinical or functional deterioration.

The probable risks of the device include stroke, arterial rupture, vascular access site complications, and other adverse events common to neurointerventional procedures.

Uncertainty in this study exists due to missing data for the primary endpoint. This finding highlights the uncertainty with the robustness of the primary outcome. However, the analysis used a missing at random (MAR) assumption for multiple imputation which was justified through a patient-level assessment of observed adverse events and outcomes. A correlation between missingness and the primary endpoint outcomes was not observed. Additional uncertainty includes the imbalance in the number of deaths observed between the test and control groups, with more deaths observed in the test group. Although the CEC determined the deaths to not be related to the Onyx LES and primarily due to the underlying SDH, for a randomized controlled study, there should be uniform baseline characteristics in the type and severity of SDH.

Additionally, patients in the EMBOLISE study were primarily treated with the Onyx LES 18 formulation while limited cases generated data using the Onyx LES 34 formulation. This disparity may introduce uncertainty with regard to the performance of the higher viscosity formulation.

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 Onyx 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 this device when used in accordance with the indications for use. The surgical cohort of the pivotal EMBOLISE clinical trial has shown that MMAE with Onyx LES as an adjunct to surgery for symptomatic subacute and chronic SDH confers substantial clinical benefit/clinically significant results with minimal additional harm/risk. These results demonstrate that MMAE with Onyx LES as an adjunct to surgery is safe and effective for

the treatment of symptomatic subacute or chronic SDH, and that the benefits are significant and outweigh the risks associated with the procedure.

XIV. CDRH DECISION

CDRH issued an approval order on December 8, 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 Onyx Liquid Embolic System (LES) during real-world use for middle meningeal artery (MMA) embolization in patients with symptomatic subacute or chronic subdural hematoma (SDH). This study will include prospective all-comers enrollment to include all subjects in whom the Onyx LES 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 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 control arm in the EMBOLISE clinical trial. Procedural information including timing of embolization with respect to surgery, device model (Onyx LES 18 vs. Onyx LES 34), 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 during the procedure, such as the access and delivery catheters, delivery syringe size, guide wire, and any adjunctive device use with Onyx LES. Follow up will occur at baseline (pre-embolization procedure), 24-48 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), 24-48 hours post-procedure (MMA embolization), 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.