SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Artificial Embolization Device

Device Trade Name: Onyx® Liquid Embolic System (Onyx® LES)

Applicant's Name and Address: Micro Therapeutics, Inc.
2 Goodyear
Irvine, California 92618

Date of Panel Recommendation: August 5, 2003

Premarket Approval Application (PMA) Number: P030004

Date of Notice of Approval to Applicant: JUL 2 1 2005

II. INDICATIONS FOR USE

The Onyx® Liquid Embolic System (hereinafter called the Onyx® LES) is indicated for the presurgical embolization of brain arteriovenous malformations (bAVMs).

III. 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.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Onyx LES labeling (Attachment 1).

V. DEVICE DESCRIPTION

Onyx® is a non-adhesive liquid embolic agent comprised of EVOH (ethylene vinyl alcohol) copolymer dissolved in DMSO (dimethyl sulfoxide), and suspended micronized tantalum powder to provide contrast for visualization under fluoroscopy. The Onyx Liquid Embolic System (LES™) consists of a 1.5 ml vial of Onyx, a 1.5 ml vial of DMSO, and three 1 ml Onyx delivery syringes. A DMSO compatible delivery micro catheter that is indicated for use in the neuro vasculature (e.g. Marathon™, Rebar™ or UltraFlow™ HPC catheters) is used to access the embolization site. Onyx is available in two product formulations, Onyx 18 (6% EVOH) and Onyx 34 (8%

EVOH). Onyx 18 will travel more distally and penetrate deeper into the nidus due to its lower viscosity compared to Onyx 34. Final solidification occurs within five minutes for both product formulations.

Onyx is delivered by slow controlled injection through a micro catheter into the brain arteriovenous malformation under fluoroscopic control. The DMSO solvent dissipates into the blood, causing the EVOH copolymer and suspended tantalum to precipitate *in situ* into a spongy, coherent embolus. Onyx immediately forms a skin as the polymeric embolus solidifies from the outside to the inside, while traveling more distally in the lesion.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Endovascular embolization of cerebral arteriovenous malformations (AVMs) as described in the literature, involves the use of catheters to deliver a variety of occlusive agents such as permanent balloons, sclerosing drugs, thrombosing coils, polyvinyl alcohol (PVA) particles, and rapidly acting glues, such as n-butyl cyanoacrylate. Currently, the most widely used embolization technique for AVMs is the injection of n-butyl cyanoacrylate.

VII. MARKETING HISTORY

The Onyx LES system was first marketed in August 1999, in Europe with the CE mark for use in the treatment of arteriovenous malformations. Onyx continues to be marketed throughout most European countries, Canada, Turkey, Australia, and some Latin American countries. Onyx has not been withdrawn from the market in any country for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

A prospective, randomized, multi-center clinical trial compared Onyx LES to the TRUFILL n-Butyl cyanoacrylate (TRUFILL) liquid embolic system for the presurgical treatment of bAVMs. The primary endpoint of the study required 100 patients to be evaluated for effectiveness. An additional 17 patients were enrolled under a continued access provision. Safety was evaluated for all 117 patients in the Intention to Treat (ITT) cohort, which includes all patients in which treatment of the assigned device was attempted. Safety was assessed based on the nature and severity of adverse events.

The safety profile for the two groups was comparable. Many of the events occurred during, or post surgery, as opposed to during, or post embolization, with the embolization agents.

Two patients died during the course of the clinical trial. Both deaths occurred in the Onyx group and both occurred following surgical resection. A third death occurred after the patient had been discharged to a rehabilitation center for persistent neurological deficits, but the patient had completed study follow-up.

The table below provides a summary of the adverse events that occurred during the study.

Table 1: Incidence of Complications

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

Incidence of Complications				
EVENT NAME	TRUFILL N=63		Onyx N=54	
Limb ischemia	2	1 (1.6%)	1	1 (1.9%)
Respiratory failure	4	4 (6.3%)	1	1 (1.9%)
Seizures	5	4 (6.3%)	1	1 (1.9%)
UTI (Urinary tract infection)	1	1 (1.6%)	1	1 (1.9%)
Vasospasm	5	4 (6.3%)	1	1 (1.9%)
Vaso-vagal episode	1	1 (1.6%)	1	1 (1.9%)
Cardiac arrhythmia/hypertension	2	2 (3.2%)	0	0 (0%)
*Embolization of unintended vessel**	7	6 (9.5%)	0	0 (0%)
*Premature polymerization time**	3	3 (4.8%)	0	0 (0%)
Vascular access complication	2	2 (3.2%)	0	0 (0%)
*Prolonged polymerization time**	5	5 (7.9%)	0	0 (0%)

[+] Patients could be counted multiple times within categories so the sum of percentages within the subcategories may not equal the total for the main category

*Technical or Procedural Event only with no clinical sequelae.

The following events occurred in one patient each in the Onyx group and did not occur in the TRUFILL group: catheter shaft rupture, delivery catheter rupture, fragmentation of Onyx, hypoxia, laryngospasm, peptic ulcer disease, psychotic episode, pulmonary edema, skin abrasion, subintimal injection, tachypnea, and tongue swelling. The following events occurred in one patient each in the TRUFILL group, and did not occur in the Onyx group: catabolic state, coagulopathy, corneal abrasion, elective carotid aneurysm surgery, high flow fistula, multi-organ system complications, myopathy/neuropathy, orthostasis, post craniotomy revision, surgical revision, transient ischemic attack (TIA), trauma, ureteral perforation, and vocal cord paralysis.

Additional adverse events, which may be associated with embolization procedures include:

- Allergic reaction
- Thrombocytopenia
- Pulmonary embolism

IX. SUMMARY OF PRECLINICAL STUDIES

Laboratory Studies

This section presents summaries of important preclinical studies in support of safety and effectiveness of the Onyx LES system. The following pre-clinical studies were conducted to ensure that the Onyx LES is safe and effective for its intended use: Mechanical/Chemical Tests, Biocompatibility Studies, and Animal Studies.

Mechanical/Chemical Tests

These tests cover the basic characterization of Onyx as a solution and as an implanted precipitate, as well as compatibility with syringes/catheters and other embolic devices, such as coils.

Study	Results and Conclusions
Tantalum Suspension	This test was performed to determine the minimum required shake time to mix and assure homogenous tantalum dispersion in Onyx. The results showed that shaking the product for 20 minutes on an Onyx mixer[1] at a setting of 8 will assure homogenous tantalum suspension. [1]Scientific Industries Genie 2, Model No. 120V SI-0240, Vial Attachment No. OA-0570-010
Onyx Solidification Time	The amount of time various formulations of Onyx took to solidify was assessed. To determine solidification time, Onyx was precipitated in saline by dispensing spherical droplets approximately 3 mm in diameter. At controlled time intervals, Onyx spheres were removed and compressed to determine if liquid could be expelled from the droplet mass. When no liquid could be expressed the material was considered solidified. The 6% and 8% formulations solidified within 3 minutes.
Material Expansion and Mechanical Properties	The purpose of the evaluation was to determine the tensile stress/strain and expansion characteristics of Onyx precipitated in saline. Tensile strength and 180 degree folding tests were performed at 1, 3 and 7 days following precipitate formation. Diameters of the rod-shaped precipitates were measured over the time course of the experiment. The diameter of the precipitates remained constant out to 7 days indicating that the material does not swell. Fold testing indicated that the material strained to the breaking point with a 180 degree bend. Tensile strength values varied from 0.5-6.0 psi with smaller diameter precipitates having higher tensile strength values.
Particulate Generation	The purpose of the study was to determine if Onyx, under simulated fluid shear conditions, generates particles in its final precipitated form. Test samples were prepared by precipitating 3-4 mm spheres of the 6% and 8% formulations in vials containing saline. The vials were inverted 20 times, the spheres removed and the fluid was analyzed with a spectrophotometer. The test results demonstrated that Onyx particulate generation was less than the maximum allowable per U.S. Pharmacopeia (USP) XXV <788> Particulate Matter for Injections.

Study	Results and Conclusions
Material Adhesion	The adhesive properties of Onyx were determined by measuring the force required to extract various catheters from a precipitated Onyx mass. The test simulated catheter entrapment that could occur due to excessive material reflux during an embolization procedure. After 60 minutes a force gauge was attached to the catheter hub and pulled at approximately 1-2 cm/sec to extract the catheter from the Onyx mass. Comparison of extraction force values of the Ultraflow and Rebar microcatheters from Onyx material, as well as comparison of extraction values of microcatheters from cyanoacrylate glue material was done. The catheters released from the Onyx mass with relatively low force as compared to the minimum tensile strength requirements of the catheters. No evidence of Onyx adhesion or fragmentation was observed. Comparison to glue-entrapped catheters demonstrated that higher extraction forces were required to release the catheters than were observed with Onyx. In addition, the speed with which entrapped catheters are pulled determines the amount of force required to release the catheter.
Effects of Radiation and Stability Onyx Precipitates	To determine if radiation could cause a chemical alteration of the Onyx material changing its biocompatibility profile or cause a degradative effect to the polymer, samples of Onyx precipitates were exposed to 30 Gray of radiation and then aged at 55°C for 210 days (2 year equivalent). The samples were tested for biocompatibility, chemical stability, and physical integrity. Cytotoxicity, acute systemic toxicity, hemolysis, and pyrogenicity evaluations showed no evidence of toxicity, hemolytic activity or change in pyrogen content. Infrared Absorption Spectroscopy and Gel Permeation Chromatography evaluations showed nearly superimposable Infrared (IR) spectra and equivalent molecular weight determinations, respectively. The test results demonstrated that Onyx was unaffected by radiation levels encountered during radiosurgery.
Infusion Pressures	To verify that infusion pressures generated during delivery of Onyx were within safe burst specification limits of the instructions for use (IFU) recommended catheters, Onyx was infused at various rates at 37°C into the UltraFlow and the Rebar micro catheters. The maximum recommended infusion rate for Onyx is 0.3 ml/min. Onyx at an infusion rate of 0.5 ml/min was considered a worst-case test. The study demonstrated that infusion rates of 0.1 to 0.5 ml/min generated infusion pressures significantly below the minimum burst specification of the IFU-recommended catheters.
Device (Catheter and Syringe) Chemical Compatibility Testing	To determine if DMSO (the active solvent in Onyx) degrades the supplied/recommended delivery devices (the UltraFlow and the Rebar micro catheters and the 1 mL syringes), chemical and functional performance of the delivery devices after exposure to DMSO was evaluated. DMSO was infused through each delivery device and then the DMSO-exposed catheters were tested for static burst and tensile strength, and the syringes for peak force and visualization of syringe barrel gradations. The test results demonstrated that delivery device strength values (burst, tensile and peak force) and visibility of the syringe barrel gradations did not degrade after extended DMSO exposure and were significantly similar to non-DMSO exposed samples. The effluent was tested (from the DMSO infusion) via High Performance Liquid Chromatography (HPLC) with comparison to the results of a pure DMSO control sample. The results showed no additional peaks other than DMSO, demonstrating that DMSO (and therefore Onyx) is chemically compatible with both recommended delivery catheters and syringes.

Study	Results and Conclusions
Adjunctive Device Compatibility (Coils and Glues)	Coil and cyanoacrylate-based embolization agents may be used in conjunction with Onyx. Metal coils were incubated with DMSO to determine if the solvent could leach any chemical from the coils. HPLC evaluations revealed no leachates. The same coils were used together with Onyx to perform an embolization of a simulated vessel. The target was occluded and no distal migration of Onyx was observed. To assess for Onyx/cyanoacrylate compatibility, a cyanoacrylate cast was first formed in a fistula simulated model. The embolic cast was then incubated with DMSO for 60 minutes. No migration of the embolic cast in the 300 mL/min fistula model was observed nor were any new peaks observed in the HPLC profile analysis.
Sterilization Validation	Dry Heat sterilization of Onyx and DMSO is performed and validated using a half cycle approach with biological indicators (BI) (consistent with EN550 and in accordance with ANSI/AAMI standard, ST63:2002, Sterilization of health care products – requirements for the development, validation and routine control of an industrial sterilization process for medical devices – dry heat) to achieve an sterility assurance level (SAL) of 10^{-6}. Ethylene Oxide Sterilization of the packaged syringes is performed and validated according to ANSI/AAMI/ISO 11135-1994, Medical Devices Validation and Routine Control of Ethylene Oxide Sterilization.
Package Integrity	The Onyx system was subjected to a Federal Express vibration and drop testing for packages 0 – 75 lbs according to ISTA 1A / D4169 following 4 days at –20°C, 29 days at 55°C and humidity less than 20% and 27 days at 55°C and 70-80% relative humidity. The test results demonstrated appropriate package integrity.
Sterile Product – DMSO and Onyx sterile barrier	To demonstrate appropriate sterile barrier, aged vials (three years accelerated aging) were subjected to pressure leak testing and were tested for sterility. No leaks were observed, and all tested samples were sterile. Based on test results, the sterile barrier vial package system for DMSO and Onyx is an effective sterile barrier.
Onyx Real Time and Accelerated Aging	The potential for the effects of aging on the performance of Onyx were evaluated by conducting accelerated and real time aging tests to support a 3-year product shelf life. The tests consisted of Leakage, Product Sterility, Cytotoxicity, Molecular Weight Distribution, Viscosity, Density, Precipitation and Extractables on Precipitation. Based on the testing results, Onyx System met the necessary criteria for a 3-year shelf life.
DMSO Real Time and Accelerated Aging	The potential for the effects of aging on the performance of DMSO were evaluated by conducting accelerated and real time aging tests to support a 3-year product shelf life. The testing consisted of analyses for impurities, including dimethyl sulfone. There were no trends in the levels or types of impurities. Based on the testing results, DMSO met the necessary criteria for a 3-year shelf life.

Biocompatibility Studies

Biocompatibility studies were performed per ISO 10993-1, Biological evaluation of medical devices for permanent implants, blood contact. Additional biocompatibility testing was performed per FDA's *Guidance on Biocompatibility Requirements for Long Term Neurological Implants.*

Summary Table: ISO 10993-1 Biocompatibility Test Results

Test Description	Title	Results
Cytotoxicity	MEM Elution Test Evaluation of Onyx	Dilution Grade* (response) 1:1 4, severe 1:2 3, moderate 1:4 0, none *tissue response severity is graded on a scale of 0-4
Cytotoxicity	MEM Elution Test Evaluation of DMSO* *Cytotoxic effects confirmed due to undiluted DMSO. Animal model evaluation determined rate of infusion to prevent DMSO cytotoxic effects (see below).	Dilution Grade (response) 1:1 4, severe 1:2 4, moderate 1:4 1, slight
Sensitization	Guinea Pig Maximization (Magnussen/Kligman Method) (Saline & cottonseed oil extracts)	Grade I, Weak sensitizer; equivalent to negative control
Intracutaneous Reactivity	USP Intracutaneous Reactivity (Saline & cottonseed oil extracts)	Passed
Acute Systemic Toxicity	USP Systemic Toxicity (Saline & cottonseed oil extracts)	Passed
Subacute Toxicity	Fourteen Day Subacute Intravenous Dosing Study (Saline extract)	Non-Toxic at 50 mL/kg/day
Implantation	USP Seven Day Muscle Implant	USP test requirements not met due to acute tissue response. Macroscopic examination revealed no difference between treated and control, however, microscopic examination showed a device-related irritant response.
Implantation	One Year Intramuscular Implant With and Without Tantalum in Rabbits	Tissue responses to Onyx with or without tantalum were greatest at earlier timepoints (30, 90 days) but then stabilized and were classified as minimal to mild inflammatory responses at one year. Microscopic examination indicates that the material (with or without tantalum) elicits a similar inflammatory response, and that over the course of the study the response gradually lessens in both cases. The test articles were not observed to migrate from the site of implantation.
Genotoxicity	Bacterial Reverse Mutation Assay (Saline and DMSO extracts)	Passed

Test Description	Title	Results
Genotoxicity	In Vitro Mammalian Cell Gene Mutation Test (Saline and DMSO extracts)	Passed
Genotoxicity	Micronucleus Cytogenic Assay in Mice (Saline and corn oil extracts)	Passed
Carcinogenicity	Carcinogenicity Using the *ras*H2 Transgenic Mouse Model	Not carcinogenic The device tested contained 8% EVOH dissolved in DMSO containing tantalum (30% w/v).

Animal Studies

The objectives of the animal studies were to evaluate the acute and chronic vascular tissue response to Onyx and DMSO, to determine device effectiveness of Onyx as an embolic occlusive agent, and to determine device biocompatibility in the subarachnoid space.

Study of angiotoxicity of DMSO in the swine rete mirabile model

The purpose of the study was to determine the injection rates and volumes of DMSO that could be safely used for delivery of the embolization agent in humans. Previous experimental investigations had shown that rapid infusion of DMSO could cause severe vascular toxicities, e.g., vasospasm, hemorrhage, angionecrosis and thrombosis. Further evaluation of DMSO associated vascular toxicity indicated that slower infusion rates minimized angiotoxicity. Twenty-six swine were infused and sacrificed at 10 and 28 days. Times of injection were 30, 60 or 90 seconds for 0.5 and 0.8 mL volumes. Saline was used as the control vehicle injected into the other rete. Vasospasm was monitored via contrast visualized angiography. A five point grading system was used to quantify the severity of vasospasm. The results indicated that a slow and controlled infusion of DMSO (anhydrous) had no severe or permanent vascular effect in the swine model. A dose rate of 0.5 mL/90 sec. (0.33 mL/min.) resulted in low vasospasm scores, low vasospasm duration times and no permanent vascular damage. At injection rates above 0.5 mL/min. gross and microscopic histopathology revealed inflammatory reactions and intimal hyperplasia.

Acute and chronic histopathological changes in the swine rete mirabile model

The purpose of the study was to evaluate the safety and effectiveness of the device as an embolization agent in the swine rete mirabile. A total of 20 swine were used in the study: the left rete was embolized with the embolic agent whereas the right rete was embolized with contrast reagent as a control. Animals were sacrificed at 3, 6 and 12 months. Prior to sacrifice an angiographic assessment of the retia was performed. The study indicated that acute and chronic specimens showed total or near total occlusion of the target rete with no evidence of endothelial denudation or arterial wall angionecrosis. The DMSO and Onyx delivery volumes and injection rates were well tolerated with no reported vasospasm, neurological deterioration, or behavioral modification post-procedure or during chronic maintenance periods. The delivery

catheters functioned as anticipated with no occlusion, rupture or adhesion type of technical problems reported. Histopathological results documented the presence of intimal hyperplasia, an inflammatory response, foreign body giant cells and focal disruption of elastica without extravasation of the material into the perivascular space at 3 and 6 months. No significant recanalization, hemorrhage or angionecrosis was reported. At 12 months, specimens exhibited a substantial decrease in the chronic inflammatory response seen at 3 and 6 months. A moderate foreign body response was observed in 4/5 specimens, however, no angionecrosis or extravasation of embolic material was observed.

Histopathology comparison of Onyx to Guglielmi Detachable Coils (GDCs)

The study series included both swine and canine animal models with experimental aneurysms surgically created on the common carotid arteries using carotid vein graft techniques. A total of 37 aneurysms in 31 animals were evaluated. Post-embolization evaluations included aneurysm occlusion, parent artery patency, procedural complications, and overall system performance. To determine if Onyx elicited a chronic tissue response equivalent to a currently approved embolic device, the investigators compared histological and pathological results of Guglielmi Detachable Coils (GDCs) to Onyx at 3 and 6-month evaluation time points. The study showed that Onyx caused an acceptable tissue response, comparable to GDC, with inflammation diminishing to mild focal collections of lymphocytes and giant cells in 12-month chronic specimens. Healthy neointimal tissue remodeling with variably mature endothelial cell growth was observed in continuity with the parent artery lumen in all Onyx treated aneurysms. The study results indicate that histological and pathological response to Onyx is acceptable and at least equivalent to the response to GDCs.

Effect of Onyx within the Cerebromedullary Cistern

The purpose of the study was to evaluate the effect of Onyx in direct contact with neurological tissue in the subarachnoid space as might occur during embolization of vascular malformations and/or the rupture of vascular embolizations during treatment with Onyx. In this experiment, rabbits were given cisterna magna injections of 6% Onyx, 25% Onyx, saline or autologous blood as controls. Each animal underwent digital subtraction angiography of the vertebrobasilar system using a microcatheter system. Animal evaluations were conducted at 2, 4, or 90 days via angiography, and gross and microscopic histopathology. There was a minimal to mild focal or multifocal vasculitis in the meninges adjacent to injected Onyx polymer on sacrifice days 2 and 4 which was characterized by necrosis of the wall of meningeal veins with slight infiltration of the wall by granulocytes. Proteinaceous exudates were observed in Onyx treated animals on days 2 and 4 and there was an increase in the incidence and severity of subacute inflammation in the meninges of Onyx treated animals. On day 90, vasculitis and proteinaceous exudates were not observed in the meninges. Degeneration/necrosis was observed in the medulla oblongata and the cerebellum and assumed two distinct patterns. Subarachnoidal distribution consisted of superficial neuropile and neuronal damage characterized by spheroids, neuronal necrosis, and gliosis. Parenchymal distribution was patchy and not associated with the surface and consisted of localized liquefaction necrosis with reactive gliosis. Parenchymal

degeneration/necrosis was of comparable incidence and severity in all groups on day 2 and was considered to be due to mechanical trauma. The distribution of changes in the cerebellum and medulla oblongata of Onyx treated animals as well as the occurrence of similar changes in the saline and blood groups (days 2 and 4 only) strongly suggest that acute pressure against the bone of the skull was involved in the pathogenesis of changes observed in the rabbit and indicate that direct toxicity of the Onyx was not a factor. Increased intracranial pressure would most likely result from the combined effects of Onyx material and associated proteinaceous fluid accumulation, and to the fact that Onyx is not resorbed or redistributed as saline or blood would be.

X. SUMMARY OF CLINICAL STUDIES

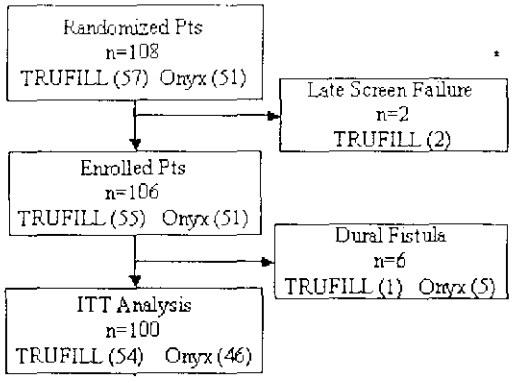
Study Purpose

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

Design

This study was designed as a prospective, randomized, multi-center clinical comparison of the MTI Onyx LES to the Cordis TRUFILL n-Butyl cyanoacrylate (TRUFILL) liquid embolic agent for the presurgical treatment of bAVMs. The primary endpoint of the study required 100 patients to be evaluated for effectiveness. One hundred and eight patients were randomized: two of these patients were late screen failures, having been deemed anatomically unsuitable for embolization by the treating physician. Thus, 106 patients were enrolled and randomized, on a 1:1 basis, at 20 clinical sites in the U.S. to either embolization with Onyx or TRUFILL resulting in 51 patients in the Onyx group and 55 patients in the TRUFILL group. Six patients were deemed by the core lab to be dural fistulae subjects, and thus were excluded from the efficacy analysis, resulting in 100 patients evaluated for efficacy. Demographic information, including bAVM characteristics, is presented on 102 patients, which includes information on the 2 patients who were late screen failures. A summary of patient enrollment is provided in Figure 1, below.

Figure 1: Efficacy Endpoint Patient Flow



*Late screen failures: anatomically unsuitable for embolization

An additional 17 patients were enrolled under a continued access provision. Safety was evaluated for all 117 patients in the Intention to Treat (ITT) cohort, which includes all patients in which treatment of the assigned device was attempted. Safety was assessed based on the nature and severity of adverse events, and is reported in Table 1. All patients with a bAVM in the cerebral cortex, cerebellum or dura mater of a Spetzler-Martin grade I-IV were randomized to either the Onyx or TRUFILL treatment arms. For patients randomized to Onyx, the formulation used (Onyx 18 alone, Onyx 34 alone, or combination of Onyx 18 and 34) was at the physician's discretion. For patients randomized to TRUFILL, the oil:TRUFILL ratio used was also at the physician's discretion. Patients underwent embolization procedure(s) to reduce the size of the bAVM prior to surgical resection. Neurological assessments (i.e., NIH scale, Barthel Index, and Glasgow Index) were performed prior to and post embolization and/or surgical resection, when surgery was performed. Although patients were to undergo total surgical resection as an enrollment criterion, 6 patients in the TRUFILL group and 5 patients in the Onyx group did not undergo total resection.

Methods

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

Inclusion Criteria

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

Exclusion Criteria

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

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

Table 2: Patient Demographics

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

Demographics include 2 late screen failure patients

Table 3: bAVM Characteristics*

(n=103 bAVMs in n=102 pts) Pretreatment Assessment		TRUFILL (n=57 bAVMs in 56 patients)		Onyx (n=46 bAVMs in 46 patients)	
bAVM Location	*Right*	55.4%	(31/56)	63.0 %	(29/46)
	Left	41.1%	(23/56)	34.8 %	(16/46)
	Midline	3.6 %	(2/56)	2.2 %	(1/46)
bAVM Located in eloquent area of Brain		48.2%	(27/56)	45.7 %	(21/46)
Venous Drainage	*Deep*	8.9 %	(5/56)	15.2 %	(7/46)
	Superficial	62.5%	(35/56)	63.0 %	(29/46)
	Both	28.6%	(16/56)	21.7 %	(10/46)
Spetzler-Martin Grade	*I*	25.0%	(14/56)	10.9 %	(5/46)
	II	25.0 %	(14/56)	43.5%	(20/46)
	III	30.4%	(17/56)	26.1 %	(12/46)
	IV	19.6%	(11/56)	19.6 %	(9/46)
bAVM Size (Core Lab, mm^3)	*Mean+/- SD*	16.0+/- 20.0		26.3+/- 45.2	
	Median	8.1		13.6	
	Range	0.08-94.9		0.17-290.5	

*bAVM Characteristics include 2 late screen failure patients

Upon enrollment, a baseline clinical neurological examination was performed and grading scales including Barthel Index, Glasgow Coma Scale (GCS) and NIH Stroke Scale (NIHSS) were recorded. In addition, baseline CT, MRI, and/or angiograms were performed for complete characterization of the bAVM prior to randomization. Following randomization, patients were embolized as deemed appropriate by the investigator. The physician determined the number of embolization stages and the percent bAVM reduction based on factors specific to each patient, such as bAVM size, number of feeders, fistulous connections, and location relative to eloquent territory. The majority of patients in each group underwent one embolization procedure. The number of embolization procedures ranged from 1 to 7, as summarized in the table below. In the Onyx group 33 patients were treated with the Onyx 18 formula, 2 patients were treated with the Onyx 34 formula and 11 patients were treated with both formulations.

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

Table 4: Embolization Procedures Per Patient

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

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

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

Effectiveness Endpoints

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

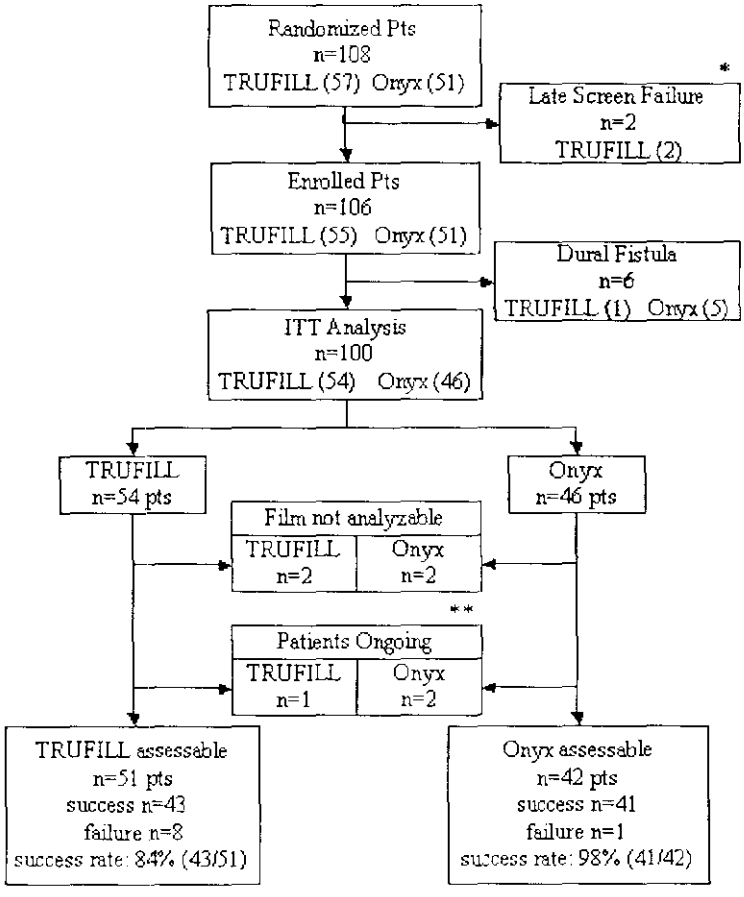
final embolization procedure.

The results for the primary effectiveness endpoint demonstrate that the two products are comparable with regard to bAVM occlusion efficacy, and thus, the primary study hypothesis (i.e., Onyx is no worse than TRUFILL in terms of bAVM obliteration defined as $\geq$ 50% occlusion as assessed by core angiographic laboratory) was achieved using an ITT approach (Table 5).

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

A summary of the ITT analysis of patient flow with results is provided in Figure 2, below:

Figure 2: ITT Analysis Flowchart



*Late screen failures: anatomically unsuitable for embolization
**Patients ongoing: continuing embolization at time of data closure

Primary endpoint analysis demonstrates non-inferiority of the Onyx device to TRUFILL. The Primary Endpoint analysis is presented in Table 5, below.

Table 5: Primary Endpoint Summary

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

Diff = Onyx – n-BCA; SE = sqrt($p_1q_1/n_1+p_2q_2/n_2$); CI = Diff±1.96*SE
RR = Onyx/n-BCA; SE = sqrt{$(1 - p_1)/ n_{11}+(1 - p_2)/ n_{21}$}; CI = RR*exp(±1.96*SE)

The study had 2 secondary effectiveness endpoints: surgical blood loss and surgical resection time. There was considerable variability in these endpoints primarily due to the complexity of this disease state and the associated surgery for resection. No statistically significant differences were observed for either of these 2 secondary endpoints.

Table 6: Secondary Effectiveness Endpoint Summary

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

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

Safety Endpoints

Safety was assessed by the nature and severity of adverse events. The adverse events are shown in Table 1.

Deaths

There were 3 deaths reported in patients treated with Onyx: two patients died during the clinical study period and 1 patient died after study follow-up was completed. In all cases, patients underwent surgical resection following embolization. The first patient

developed intra- and peri-operative bleeding which resulted in a hematoma and infarction. The patient expired following withdrawal of care. The second patient had a large post-surgical middle cerebral artery (MCA) infarction and expired following withdrawal of care. The third patient who died following study follow-up completion sustained a significant neurological deficit after a surgery-related hemorrhage and required long term skilled nursing home care. The patient died several months after discharge in the nursing home.

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

The technical/procedural events encountered during embolization were similar for the two groups except for delivery catheter removal difficulty, which occurred 6 times in 5 patients in the Onyx group and in only 1 patient in the TRUFILL group. All catheters in the Onyx group were able to be removed. The catheter in the TRUFILL group remained in the patient. Table 7, below, summarizes the technical/procedural events related to the respective embolic agents:

Table 7: Technical/Procedural Events – Embolic Agent*

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

*Includes 17 continued access patients

Additional Clinical Experience

Histopathology Study of AVMs Embolized with Onyx:

To assess Onyx for potential chronic histotoxic effects, 7 bAVMs embolized with Onyx were surgically excised from human subjects and submitted for evaluation to a board certified histopathologist. The patients were treated in studies unrelated to this clinical trial. The time from treatment with Onyx to surgical excision ranged from 3 to 19 months. Histopathological findings generally indicated successful embolization of AVM feeders and reduction of AVM size without ischemic or hemorrhagic complications. There were no indications of vascular necrosis, rupture or extravasation of the Onyx material. Numerous vessels were observed with disruption of the internal elastic lamina, but there did not appear to be any serious adverse effect on the vessel wall. There were frequent indications of small diameter reformed vascular lumens characterized by endothelialization over well organized masses of Onyx material, but no evidence of actual recanalization. bAVM embolization with Onyx did not appear to be definitively associated with any morphologic changes that would be expected to produce adverse clinical sequelae.

MRI/CT Evaluation of AVMs treated with Onyx or n-BCA:

A retrospective, masked review was conducted on Onyx and n-butyl cyanoacrylate (n-BCA) patients to determine if any direct neurotoxicity was detected in the brain post-AVM embolization using current imaging methods. The patients were treated in studies unrelated to this clinical trial. A central reader reviewed pre- and post-embolization MRI or CT scans, from 73 patients. Fifty-four AVM patients were treated with Onyx and 19 AVM patients were treated with n-BCA. All MRI and CT studies were evaluated for the presence or absence of gliosis, encephalomalacia, edema, leptomeningeal or parenchymal enhancement and hemorrhage. The study indicated that there is no imaging evidence that these embolic devices are associated with cerebral imaging abnormalities.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

The biocompatibility assessments and toxicology information indicate that the materials used in the Onyx® LES product are safe. A comprehensive list of evaluations was conducted to assess the potential of the embolization agent to elicit cytotoxicities or adverse tissue responses. Although some mild to moderate toxicities were observed in certain tests, e.g., the cytotoxicity assessments and the acute observations of the implantation evaluations, the adverse findings lessened over time. The device was evaluated in a number of animal models investigating the short term and long term vascular biocompatibility and the potential for the material to cause adverse effects if it were to gain access outside of blood vessels. Investigation found that a controlled, slow infusion of the composite product was necessary to avoid DMSO-mediated vascular toxicities. With controlled delivery, the device was observed not to elicit angionecrosis but did cause a foreign body response at acute time periods that persisted out to 12 months. The foreign body response does not appear to be significantly different than other embolization agents, e.g., a comparative study of coils to Onyx® in an aneurysm model noted equivalent tissue responses.

Product specifications have been identified and validated to ensure the manufacture of product of consistent quality. The specifications are product benchmarks that assess product characteristics which are essential to device performance.

The clinical study compared the effectiveness and safety of the Onyx® LES to an approved bAVM embolization agent, the TRUFILL® LES. Onyx® was found to effectively embolize AVMs and to perform equivalently to the TRUFILL® product. Similarly for secondary effectiveness endpoints, the 2 products caused the same approximate degree of blood loss and the procedures were approximately the same length of time. With regard to safety, the incidence and degree of adverse events observed for the cohorts was similar. Although all deaths that occurred during (2), or after study (1) were in the treatment group, no device causality was established. There were more difficulties in removing catheters in Onyx®-treated patients than of TRUFILL®-treated patients.

In conclusion, results from preclinical studies indicate that the materials used in Onyx® LES are safe. Multi-center clinical data have provided reasonable assurance of the safety and effectiveness of the Onyx® LES when used in accordance with the labeling.

Therefore, it is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

XII. PANEL RECOMMENDATION

At an advisory meeting held on August 5, 2003, the Neurological Devices Panel recommended that Micro Therapeutic's PMA for the Onyx Liquid Embolic System be approved subject to submission to and approval by, the Center for Device and Radiological Health (CDRH) of the following:

1. Labeling revised to include a statement that there were more instances in which the user had difficulty removing the delivery catheter for the Onyx device than for the control, n-BCA device.

2. Labeling revised to include a statement that all study fatalities occurred in the Onyx® LES group, and that while these deaths could not be attributed to the device, the possible role of Onyx® LES in the patient's death, if any, is unknown.

3. MTI should submit data from a study of angiotoxicity and vasculitis in surgically excised Onyx® LES specimens and in a small number of post-mortem samples.

4. MTI should make a concerted effort to collect and report Onyx® LES European data to the FDA.

5. Evidence of hemolysis in a small human patient cohort should be investigated.

6. A plan for collection of data for patients who did not have their AVM completely, surgically resected. Patients will be followed for 3 years, post-embolization.

7. The mandatory training program that would include the following elements:

    - Hands-on training using in vitro and in vivo models under fluoroscopic visualization

    - Newly trained physicians must have one proctored case; if the physician's first case is deemed a failure, the physician must conduct another proctored case.

XIII. CDRH DECISION

CDRH reviewed the Neurological Devices Advisory Panel's recommendations of August 5, 2003. To address the labeling revision conditions, Micro Therapeutics provided revised labeling incorporating the Panel's recommendations regarding catheter removal difficulties and the incidence of death in the Onyx patient group. FDA considered requesting histo-pathological examinations from a small number of explanted samples but considered the

human data previously provided by the sponsor, i.e., 7 explanted samples, sufficient. FDA believes the data from this study provides reasonable assurance of safety and effectiveness and does not believe that European surveillance data are necessary. FDA considered the information provided in this clinical study adequate to address potential concerns regarding DMSO-mediated hemolytic effects. The study did not reveal any significant trends of hemolysis and so an additional small study was thought to be unnecessary. Micro Therapeutics has agreed to follow patients who did not undergo surgical resection for 3 years post-embolization and they provided the training program that all sites will participate in prior to independently using the Onyx Liquid Embolic System.

FDA issued an approval order on JUL 2 1 2005 .

The applicant's manufacturing facilities were inspected on June 12, 2003 and were found to be in compliance with the Quality System Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

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

Post approval Requirements and Restrictions: See approval order.