

SUMMARY OF SAFETY AND EFFECTIVENESS DATA**I. GENERAL INFORMATION**

DEVICE GENERIC NAME: Artificial Embolization Device

DEVICE TRADE NAME: TRUFILL® n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System, containing: TRUFILL® n-Butyl Cyanoacrylate (n-BCA), TRUFILL® Ethiodized Oil and TRUFILL® Tantalum Powder

APPLICANT: Cordis Neurovascular, Inc.
14000 NW 57th Court
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PREMARKET APPROVAL APPLICATION (PMA): P990040

DATE OF PANEL RECOMMENDATION: May 11, 2000

DATES OF GMP INSPECTION: January 10-14, 19, 20, 2000

DATE OF NOTICE OF APPROVAL OF APPLICATION: SEP 25 2000

EXPEDITED REVIEW: Expedited processing was authorized on October 15, 1998, based on the potential of the TRUFILL® n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System to provide a clinically important advance over existing alternatives in the embolization of arteriovenous malformations when presurgical devascularization is desired.

II. INDICATIONS FOR USE

TRUFILL® n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System is indicated for the embolization of cerebral arteriovenous malformations (AVMs) when presurgical devascularization is desired.

III. DEVICE DESCRIPTION

The TRUFILL® n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System is an artificial embolization device, comprised of TRUFILL® n-Butyl Cyanoacrylate (n-BCA), TRUFILL® Ethiodized Oil and TRUFILL® Tantalum Powder. These components must be used as a system. They are not intended to be used as individual components. The TRUFILL® n-BCA Liquid Embolic System is used under fluoroscopic guidance to obstruct or reduce the blood flow to cerebral arteriovenous malformations (AVMs) via superselective catheter delivery. Upon contact with body fluids or tissue, the mixture polymerizes into a solid material.

The TRUFILL® n-BCA monomer is a clear, free-flowing liquid that polymerizes via an anionic mechanism. TRUFILL® Ethiodized Oil is a straw to amber colored, oily fluid containing iodinated poppyseed oil used as a radiopaque polymerizing retardant. The amount of TRUFILL® Ethiodized Oil used will vary the rate of polymerization of TRUFILL® n-BCA. TRUFILL® Tantalum Powder is a finely ground, irregularly shaped, dark gray metal that may be used with TRUFILL® Ethiodized Oil to radiopacify TRUFILL® n-BCA.

IV. CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and TRAINING

CONTRAINDICATIONS

SEPARATE USE OF THE INDIVIDUAL COMPONENTS OF THE TRUFILL® N-BCA LIQUID EMBOLIC SYSTEM IS CONTRAINDICATED. THESE COMPONENTS MUST BE USED AS A SYSTEM.

TRUFILL® ETHIODIZED OIL ALONE SHOULD NOT BE INJECTED:

- **INTRAVASCULARLY**
- **INTRATHECALLY**
- **INTRABRONCHIALY.**

The use of the TRUFILL® n-BCA Liquid Embolic System is contraindicated when any of the following conditions exist:

- When optimal catheter placement is not possible.
- When a previous history of reactions to cyanoacrylates exists.

- When a previous history of hypersensitivity to ethiodized oil exists.
- When a previous history of reactions to iodine exists.
- When provocative testing indicates intolerance to the occlusion procedure.
- When vasospasm stops blood flow.

WARNINGS

- The safety and effectiveness of the TRUFILL® n-BCA Liquid Embolic System as a long-term implant has not been established.
- Performing therapeutic embolizations to occlude blood vessels is a high risk procedure. The procedure should be carried out under the direction of personnel with interventional training and thorough knowledge of angiographic techniques.
- Therapeutic embolization should not be performed when high blood flow precludes safe infusion of embolic agent.
- Fluoroscopic determination of the radiopacity of the TRUFILL® n-BCA Liquid Embolic System by comparison with a similar syringe containing contrast prior to injection is essential. Inadequate visualization of the n-BCA mixture may cause inappropriate embolization.
- TRUFILL® n-BCA is a fast-setting adhesive capable of adhering to most body tissues. It will polymerize in the presence of anionic media, such as any body fluids or tissues. Proper handling is required to avoid premature polymerization and occlusion of the delivery system or adherence of the catheter tip to the vessel wall.
- TRUFILL® Ethiodized Oil should NEVER be used as a radiopaque contrast agent to assess hemodynamics and should be used ONLY to prepare the TRUFILL® n-BCA Liquid Embolic System.
- AVM embolization may influence blood flow patterns, thereby subjecting arteries supplying the AVM or the brain proximal to the AVM to increased pressures. Increased arterial pressures could result in hemorrhagic complications.
- Laboratory studies have determined that TRUFILL® Ethiodized Oil may elute from the device over time.

- Life threatening and fatal reactions may occur without warning. At all times a fully equipped emergency cart and resuscitation equipment should be readily available, and personnel competent in recognizing and treating reactions of all severity should be on hand.

PRECAUTIONS

- Store in a cool, dark, dry place.
- Do not use if package is open or damaged.
- Use prior to "Use Before Date".
- Angiography is necessary for pre-embolization evaluation, operative control and post-embolization follow-up.
- Verify that the TRUFILL® n-BCA is a clear and free-flowing liquid prior to use. Material that is thickened or discolored should be discarded. It is recommended to use a 21 or 23 gauge needle to aspirate the TRUFILL® n-BCA into an appropriate injection syringe.
- TRUFILL® n-BCA will adhere to most surfaces. Avoid contact with non-disposable surfaces or surfaces that can not be cleaned with acetone.
- Gloves and eye/face protection are recommended when handling TRUFILL® n-BCA.
- Verify that the catheters and accessories used in direct contact with the TRUFILL® n-BCA are clean and compatible with the material and do not trigger polymerization or degrade with contact. Refer to "Accessories" under the "Recommended Procedure" section of these Instructions for Use.
- Do not use with any device containing polycarbonate. Cyanoacrylates cause polymers containing polycarbonate to deteriorate.

TRAINING

Serious, including fatal, consequences could result with the use of the TRUFILL® n-BCA Liquid Embolic System without adequate training. Contact your Cordis Neurovascular, Inc sales representative for information on training courses.

V. POTENTIAL ADVERSE EVENTS

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

Table 1

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

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

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

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Transarterial embolization of cerebral arteriovenous malformations (AVMs), using various occlusive agents, has been described since the 1960s. Cyanoacrylates were first used to treat cerebral AVMs in the mid-1970s. Isobutyl 2-cyanoacrylate was used initially but was replaced in the 1980s by n-Butyl cyanoacrylate. n-Butyl cyanoacrylate is commonly used within and outside the United States to treat cerebral AVMs.

Polyvinyl Alcohol (PVA) particles have also been available since the mid-1970s. They too are commonly used to treat cerebral AVMs, particularly in the absence of high-flow rates.

Embolic coils are frequently used in conjunction with n-BCA and PVA to treat cerebral AVMs. They are often used to reduce flow prior to injection of either n-BCA or PVA.

VII. MARKETING HISTORY

The TRUFILL® n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System, comprised of TRUFILL® n-Butyl Cyanoacrylate (n-BCA), TRUFILL® Tantalum Powder, and TRUFILL® Ethiodized Oil has not been previously commercially available anywhere.

VIII. SUMMARY OF PRE-CLINICAL STUDIES

This section provides brief summaries of important preclinical tests performed on components of the TRUFILL® n-BCA Liquid Embolic System or the entire device, i.e., n-BCA, ethiodized oil and tantalum powder, itself (Table 2).

Table 2

n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System Pre-Clinical Studies

Development & Characterization Studies	
Study	Results/Conclusions
Catheter Compatibility	Regatta and Prowler 10 microcatheters were tested with the n-BCA/ethiodized oil/tantalum powder mixture to demonstrate catheter compatibility. Two different ratios of n-BCA to ethiodized oil were evaluated: a high ratio of n-BCA to oil (50:30) and a low ratio of n-BCA to oil (20:60). The concentration of tantalum was kept constant. The mixtures were injected through the catheters and the polymerization rates pre and post injection were compared. The integrity of the catheter was assessed post-injection by conducting a catheter pull test. All of the catheters tested passed the acceptance criteria, i.e., all post-injection pull testing of the catheters had a minimum break force of 100 g and post-catheter transit polymerization time of the mixture was less than 1 second (high glue ratio) or equal to the pre-catheter transit polymerization time (high oil ratio).
Repeatable Polymerization Rate – Polymerization Time	To determine the polymerization rate and time of n-BCA, the glue was applied via droplets to the surface of bovine plasma. Polymerization time was noted when the entire drop became opaque. All samples polymerized within the acceptance criteria of less than or equal to one second.
Polymerization Rate – Animal Studies	Physicians evaluated the polymerization rate of the device (n-BCA, tantalum and ethiodized oil) in an in vivo model. The polymerization was reported as predictable and accurate in qualitative assessments.
Hydrolytic Degradation Test	n-BCA embolic agent was mixed with ethiodized oil and tantalum powder in a 1:3:1 ratio (the most common ratio used in clinical study) and polymerized in a bovine plasma solution. The material was then incubated in PBS at 50°C for 7 and 15 days and the incubation medium was then analytically evaluated. Formaldehyde, P-toluene sulfonic acid (p-TSA), and sulfurous acid were not detected in any samples. Tantalum, cyanoacetic acid, cyanoacetate, cyanoacrylate also were not detected in any samples. Butylated hydroxyanisole and butanol were detected in low ppb and low ppm amounts, respectively.

<p>Elution Test</p>	<p>The n-BCA embolic agent was mixed with ethiodized oil and tantalum powder in a 1:3:1 ratio and polymerized in a bovine plasma solution. The material was then incubated in PBS at 37°C for 4 and 10 days. An additional study on a 9:1 ratio of oil to glue was conducted to evaluate a maximized combination of oil to glue. An unknown oil-based analyte eluted from the material and was detected for both ratios. Minimal amounts of Ethiodized Oil, up to 14 ppm at 10 days, eluted from the 1:3:1 mixture. In comparison, up to 38 ppm of Ethiodized Oil and/or components eluted within 10 days from the 9:1 oil to n-BCA mixture.</p> <p>Although low quantities (ppm) were observed eluting from the device, the results were cause for a Warning statement to be placed in the Instructions for Use: “Laboratory studies have determined that TRUFILL® Ethiodized Oil may elute from the device over time.”</p>
<p>Tantalum Powder Suspension Test Validation</p>	<p>The purpose of this validation was to qualify the Tantalum Powder suspension test in Ethiodized Oil with n-Butyl Cyanoacrylate (n-BCA) polymeric material. The Tantalum Powder suspension video image was compared to its fluoroscopy image to ensure that the video image is representative of the image seen in fluoroscopy.</p> <p>The validation demonstrated that video images and fluoroscopy images of the Tantalum Powder mixed with Ethiodized Oil and n-BCA as compared with Ethiodized Oil alone, were comparable in homogeneity and intensity of radiopacification within the specified time of 1 minute. The Tantalum Powder/ n-BCA/ Ethiodized Oil mixture could be aspirated in a 27-gauge needle and the Tantalum Powder fell like sand without any clumping within the mixture.</p>

<p>USP Physicochemical Testing</p> <p>n-BCA</p> <p>Tantalum Powder</p>	<p>The n-BCA test extract passed all USP limits (non-volatile residue, residue on ignition, heavy metals, buffering capacity).</p> <p>The Tantalum Powder test extract passed all USP limits (non-volatile residue, residue on ignition, heavy metals, buffering capacity). However, due to the nature of the material, extraction conditions were based upon weight rather than the USP specified surface area and therefore USP limits may not apply.</p>
<p>Sterile Product – Pouch Sealing Validation</p>	<p>The purpose of this test was to ensure that environmental conditions or sterilization did not adversely affect the packaging sealing process. The n-BCA and Tantalum Powder are packaged in Tyvek/Mylar pouches using a heat sealing process. The pouch is impulse heat sealed using a modified Vertrod Thermal Sealer with different temperature alarms. After the heat sealing process is completed, the Tantalum Powder and n-BCA samples are sterilized using Gamma Radiation and EtO sterilization, respectively. Visual inspection and Burst Testing are then conducted on all units. All units tested met the visual and burst test acceptance criteria. All seals were free from damage (burns, wrinkle, etc.). In addition, the burst pressure lower tolerance limit and average for each run were above the pouch burst specification.</p>
<p>Sterilization Validation (Product)</p>	<p>Dry Heat sterilization of n-BCA is performed and validated according to the ANSI/AAMI ST 40 Guidelines using an Overkill method to achieve an SAL of 10^{-6}.</p> <p>Gamma irradiation of Tantalum Powder is performed and validated according to AAMI/ISO 11137 Method I, using an Overkill method to achieve an SAL of 10^{-6}.</p> <p>Ethylene Oxide Sterilization of Package is performed and validated according to ANSI/AAMI/ISO 11135-1994, Medical Devices Validation and Routine Control of Ethylene Oxide Sterilization.</p>

<p>Not Affected by Environmental Conditions/Transportation Package Integrity Test</p>	<p>The purpose of the test was to ensure that the integrity of the device components was not adversely affected by environmental/transportation conditions. The device components were assessed via the following tests: Polymerization time; Tantalum suspension in n-BCA; Viscosity and appearance; Composition analysis of n-BCA; Pouch burst testing; Self piercing luer cap; Label visual and peel testing; and Visual test – dispenser box, particle size consistency, tantalum powder pouch seal cap strength and tantalum powder/n-BCA interaction. The results demonstrated package integrity and product stability.</p>
<p>Convenient Accessibility – Self Piercing Luer Cap Test</p>	<p>The purpose of this test was to ensure that n-BCA could be accessed readily and easily by the physician. Self-piercing caps must screw onto tubes easily, perforate the aluminum tubes and allow free flow of glue without any leaks from the base of the cap. The self-piercing caps met the acceptance criteria. They screwed onto the tubes easily, perforated the aluminum tubes and allowed free flow of glue without any leaks from the base of the cap.</p>
<p>Shelf Life – Accelerated Aging (n-BCA and Tantalum Powder)</p>	<p>The purpose of this test was to evaluate the effects of aging on the performance of TRUFILL® n-BCA, Tantalum Powder and packaging components. Accelerated aging testing was conducted to support a 2-year shelf life for n-BCA and a 3-year shelf life for the Tantalum Powder. The tests consisted of Chemical Testing, Appearance Testing, Viscosity Testing and Polymerization Testing for n-BCA and Tantalum Suspension in n-BCA, Particle Size/Composition, Packaging Performance, Cap Removal, Packaging (Visual) and Visual of Product for Tantalum Powder. Based on the testing results, n-BCA met the necessary criteria for a 2-year shelf life. The test results of the Tantalum Powder met the necessary criteria for a 3-year shelf life.</p>
<p>Shelf Life – Real Time Studies (n-BCA and Tantalum Powder)</p>	<p>The purpose of this test was to evaluate the ability of n-BCA, Tantalum Powder and packaging components to withstand real time product aging after sterilization for a 3-year period without a significant change in performance of the product or loss of sterile packaging integrity, when stored in a controlled environment. Shelf life testing conducted confirmed that all the performance and purity analysis specifications were met by the n-BCA after 3-years shelf life.</p>

Table 2 (cont.)

**n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System Pre-Clinical Studies/
Toxicology Studies**

The following tests* were conducted on the individual components (n-BCA and tantalum powder) and/or on the entire device (n-BCA, tantalum powder, ethiodized oil) as it is intended to be used.	
Study	Results/Conclusions
Cytotoxicity:	
n-BCA	Pass, non-cytotoxic.
Tantalum Powder	Pass, non-cytotoxic.
Entire Device	Pass, non-cytotoxic: mild signs of cellular reactivity (Grade 2 on a scale from 0 to 4) were noted.
Intracutaneous Toxicity:	
n-BCA	Pass, non-irritant.
Tantalum Powder	Pass, non-irritant.
Entire Device	Pass, non-irritant.
Kligman Maximization Study (sensitization assays):	
n-BCA	Pass, non-sensitizer.
Tantalum Powder	Pass, non-sensitizer.
Entire Device	Pass, non-sensitizer.
Systemic Toxicity:	
n-BCA	Pass, non-toxic.
Tantalum Powder	Pass, non-toxic.
Entire Device	Pass, non-toxic.

<p>Hemocompatibility:</p> <p>n-BCA (direct contact with uncured n-BCA)</p> <p>Entire Device (direct contact with uncured n-BCA)</p>	<p>Most hematologic parameters (counts of WBC, RBC, and Platelets, Hct %, MCV, MCH, MCHC) assessed indicated no difference between treatment and control. Blood incubated with the subject device contained 18.5% plasma free hemoglobin in comparison to 4.7% for the negative control.</p> <p>The device caused a decrease in platelet counts and an increase in plasma free hemoglobin.</p>
<p>Hemolysis:</p> <p>n-BCA (direct contact with cured n-BCA)</p> <p>Tantalum Powder</p> <p>Entire Device (direct contact/in situ polymerization and hemolysis measurement)</p>	<p>Pass, non-hemolytic (The test article caused a hemolysis value of 1%. Under the conditions of the study the device is considered non-hemolytic (passing criterion is set at <5% hemolysis)).</p> <p>Pass, non-hemolytic</p> <p>Pass, non-hemolytic (The device caused 1.31% hemolysis).</p>

<p>Implantation:</p> <p>n-BCA</p> <p>Tantalum Powder</p> <p>Entire Device</p>	<p><u>7 days:</u> macroscopically not significantly different than control (PVA particles were used as the control and showed an insignificant macroscopic reaction); microscopically classified as a severe irritant: the test sites showed substantial acute and chronic granulomatous inflammation with necrosis.</p> <p><u>30 days:</u> macroscopically not significantly different than control (insignificant macroscopic reaction); microscopically classified as a moderate irritant: marked chronic granulomatous inflammation</p> <p>Pass</p> <p>Macroscopic evaluation of the test article implant site indicated that the device was non-toxic. Microscopic analysis of the implantation site at 28 days revealed slight toxicity.</p>
<p>Subchronic Toxicity: (14 day repeat dose (I.V. injection) toxicity study)</p> <p>Entire Device</p>	<p>Pass, non-toxic.</p>
<p>Genotoxicity Ames Mutagenicity:</p> <p>n-BCA</p> <p>Entire Device</p> <p>Bone Marrow Micronucleus: Entire Device</p> <p>Mouse Lymphoma Mutagenesis: Entire Device</p>	<p>Pass, non-mutagenic.</p> <p>Pass, non-mutagenic.</p> <p>Pass, non-mutagenic.</p> <p>Pass, non-mutagenic.</p>

Pyrogenicity:	
n-BCA	Pass, non-pyrogenic.
Tantalum Powder	Pass, non-pyrogenic
Entire Device	Both the extracted device and the control plasma (alone) elicited a febrile response in the animals. The investigators concluded that the bovine plasma may have caused the temperature rise. The absolute temperature increases were from 0.1°C to 0.3°C.

* Tests were done under standardized conditions that included saline and cottonseed oil extractions. The entire device was tested using the following protocol: A total of 3-4 g mixture was used for extraction in about 20 mL of medium for each test. 1 cc of n-BCA, 1 g of Tantalum Powder and 2 cc of Ethiodized Oil was mixed to produce a mixture and was polymerized in 3-4 mL of bovine plasma.

Conclusions from Pre-clinical Studies

The non-clinical laboratory studies performed in the development and evaluation of the TRUFILL® n-BCA Liquid Embolic System have established that the device is Cordis Neurovascular, Inc. catheter-compatible (excepting polycarbonate containing catheters) and that the device, components alone or together, do not cause an overtly toxic tissue response. In fact biocompatibility tests showed that the material(s) do not induce a mutagenic, pyrogenic, grossly hemolytic, sensitizing, irritating or cytotoxic effect. Elution studies demonstrated that ethiodized oil can be expected to elute from the implanted device in parts per millions quantities over time. The safety and effectiveness of the TRUFILL® n-BCA Liquid Embolic System as a long-term implant has not been established. As recommended by the Panel, the labeling contains a Warning regarding long-term implantation.

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IX. SUMMARY OF THE RESULTS OF THE CLINICAL INVESTIGATION

The following is a summary of the clinical study designed to determine if the TRUFILL® n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System is as safe and effective as conventional treatment for the obliteration of cerebral arteriovenous malformations (AVMs) when preoperative devascularization is desired. Conventional treatment was defined as pre-operative embolization with polyvinyl alcohol particles (Cordis Endovascular System's TRUFILL® PVA).

Study Design

A prospective, multi-center, single-blind, randomized study was conducted to verify that the TRUFILL® n-BCA Liquid Embolic System is as safe and effective as polyvinyl alcohol particles (TRUFILL® PVA) for use in the obliteration of cerebral AVMs when pre-surgical devascularization is desired. For patients requiring staged embolizations, the initial randomization assignment to treatment was kept consistent.

Patients enrolled in the study were those who had an AVM that required preoperative devascularization as determined angiographically. Patients with Spetzler-Martin grade III, IV and V AVMs were treated, and patients with grade I and II lesions were treated if they met the following criteria: the anticipated benefit of the embolization was greater than the risk of the embolization procedure; and the AVM feeding pedicle was located in an area that was difficult to surgically access. Patients who had been embolized with PVA or cyanoacrylate previously and patients with a known sensitivity to iodine containing contrast reagents, e.g., Iodothalamate, were excluded from the study.

Pre-embolization evaluations included angiography, a neurological evaluation, and vital sign measurements. A study-related medical/surgical history and physical examination were also performed. Conjunctive therapy using coils was permitted prior to embolization to slow the flow rate (if needed) or if a portion of the AVM contained blood vessels that were larger than the largest size of PVA available.

A post-embolization angiogram and neurological examination were performed. The neurological examination was repeated prior to surgery only if a permanent deficit occurred post-embolization. The angiogram and neurological examination were repeated prior to discharge.

This was a single-blind study. The pre- and post-embolization NIH Stroke Scale neuro-evaluations were performed by a practitioner not involved in the study who was blinded as to the treatment the patient received. The injection of the embolic agent however could not be blinded since the embolic materials are visually very different and require different delivery techniques. In order to control bias, the pre-and post-embolization angiograms were sent to a core lab to document the percent of nidus reduction and the number of feeding vessels obliterated. Due to the nature of the two different occlusive

agents (PVA and n-BCA) the core lab was able to distinguish which occlusive agent was used.

Study Endpoints

The primary effectiveness outcome was the degree of intended vascular occlusion (percent nidus reduction and number of feeding vessels being treated) after the embolization procedure. Angiographic assessment was performed at an angiographic core laboratory. Secondary effectiveness outcomes were the length of time to resect the AVM and surgical blood loss, as reflected by the number of transfusions and volume of fluid/colloid replacement required during surgery. Adverse events, complications and unanticipated adverse device effects experienced by patients in the PVA and n-BCA groups were tabulated and compared for the safety endpoint.

Results

Baseline Demographics

Approximately 59% of the subjects were male and 41% female. The majority of subjects (78%) were Caucasian. There were no statistically significant differences in demographics between treatment groups.

Patient Accounting

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

Primary Effectiveness Results

The primary effectiveness endpoint was the degree of vascular occlusion (percent nidus/lesion reduction and number of vessels occluded). Staged embolizations (more than one embolization procedure per subject) were allowed. The mean percent reduction in lesion volume and number of feeding vessels occluded per subject and per stage are listed in the following table 3. The value of N provided in parentheses represents the number of patients or stages without missing data that were used for the effectiveness analyses.

Table 3

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

Secondary Effectiveness/Safety Results

Additional parameters assessed included the time of resection and the blood volume replacement needed (units of blood, fluid/colloid, or amount from cell saver). Results for the time of resection and blood volume replacement are reported below in Table 4 below. This table displays results on a per procedure basis (105 total). In order to capture data collected for subjects who underwent unanticipated multiple resections, a per procedure assessment was necessary.

Table 4**Summary of Data During Surgery-Time to Resect AVM and Volume Blood Replacement Needed**

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

⁺ One n-BCA subject underwent multiple resections.

^{*} Two PVA subjects underwent multiple resections. One subject had an aborted resection after the dura was opened, then underwent true resection at a later date.

* In addition, one crossover subject (PVA to n-BCA) was not resected.

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

Treatment Failures

There were nine subjects who were considered treatment failures (four n-BCA, five PVA).

n-BCA

Four subjects randomized to n-BCA were considered treatment failures. Two subjects were discontinued due to "inability to subselect vessel," and two patients received n-BCA initially and then the embolization was completed using PVA. Two additional subjects in the n-BCA group did not receive n-BCA but were not considered device failures. No attempt was made to embolize one subject's AVM due to an unsafe location, and another subject received coils during the first stage but withdrew from the study prior to the second stage.

PVA

Five subjects randomized to PVA were considered treatment failures. Two of the treatment failures were crossover subjects, one received n-BCA off-study, and two had coils used post-embolization.

The two crossover subjects were both randomized to PVA, were considered treatment failures, and subsequently received treatment with n-BCA. Another subject was randomized to PVA and completed the study as planned, but then suffered a post-operative bleed and was treated successfully with n-BCA. Two subjects in the PVA group were considered treatment failures due to use of coils post-embolization.

Unanticipated Adverse Device Events (UADE)/Deaths

One UADE was reported for a subject in the n-BCA group. A small amount of glue refluxed into the proximal middle cerebral artery and embolized into branches of the middle cerebral artery. This event resulted in permanent disability and extension of hospitalization, and was determined to be probably related to the device.

Four subjects died during the study, two during the treatment period (one n-BCA, one PVA) and two after AVM resection (two PVA). The two subjects who died during the treatment period died because of cerebellar hemorrhage (n-BCA) and intracerebral hemorrhage (PVA). The treatment period was defined as from presurgical embolization up through surgical resection.

X. CONCLUSIONS DRAWN FROM THE STUDY

This study provides reasonable assurance of the safety and effectiveness of TRUFILL® n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System for the treatment of cerebral AVMs when presurgical devascularization is desired.

XI. PANEL RECOMMENDATION

On May 11, 2000 the Neurological Devices Advisory Panel recommended approval with conditions of Cordis Neurovascular's PMA for the TRUFILL® n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System. The four conditions of approval recommended were:

1. The labeling should contain the following statement; the safety and effectiveness of the TRUFILL® n-BCA Liquid Embolic System as a long-term implant has not been established.
2. The labeling should contain language that specifies that the clinical studies were done with the amount of n-BCA used varying from 10 to 70 percent.
3. Physicians should undergo training prior to using the material.
4. The results of ongoing preclinical device testing should be reported to FDA and FDA should evaluate the results prior to approving the PMA.

XII. CDRH DECISION

FDA granted expedited review status for the sponsor's application on October 15, 1998 and accepted the sponsor's application for PMA modular review on December 2, 1998. The PMA was filed on July 16, 1999 and the Neurological Devices Panel of the Medical Devices Advisory Committee reviewed and voted, 4-2, to approve the application on May 11, 2000.

The recommendations provided by the panel were addressed. Specifically, the labeling contains a statement regarding the lack of long-term biocompatibility testing and also includes information regarding the ratio of n-BCA to ethiodized oil evaluated in the study. Recommendations for n-BCA/ethiodized oil mixing ratios are provided for the user. The labeling also contains recommendations for the user to undergo training prior to using the material and Cordis Neurovascular, Inc. provides a training program for physicians. The remaining outstanding preclinical testing and product manufacturing issues were submitted after the panel meeting and were reviewed by FDA. These issues involved assessing the results of the entire device biocompatibility testing, hydrolytic degradation and elution evaluations, and additional mutagenicity testing. The safety

profile demonstrated for the entire device was found to raise no new concerns over the biocompatibility test results of the individual components.

Inspection of the sponsor's manufacturing facilities was completed and a letter was issued on July 28, 2000 stating that the manufacturer was found to be in compliance with the device Good Manufacturing Practice regulations.

FDA issued an approval order on September 25, 2000

XIII. APPROVAL SPECIFICATIONS

Directions for Use: See product label.

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

Postapproval Requirements and Restrictions: See Approval Order.