

Preclinical Review
P030004

DATE: 7/10/03

Recommendation/summary comments:

Onyx, manufactured by Micro Therapeutics, Incorporated, is a polymeric embolization agent intended for use in the presurgical embolization of brain arteriovenous malformations. It is similar to a recently FDA-approved polymeric embolization agent, the Trufill n-Butyl Cyanoacrylate (n-BCA) Liquid Embolic System manufactured by Cordis Neurovascular, Inc. in that the material polymerizes, or in the case of Onyx, precipitates, in situ. Its composition and chemical characteristics are distinctly different from the n-BCA product. Polymeric embolization agents join the family of other artificial embolization agents that include particulate embolic agents, coils, and balloons. Onyx is a mixture of ethylene vinyl alcohol copolymer (EVOH) dissolved in dimethyl sulfoxide (DMSO). Micronized tantalum powder is suspended in the liquid polymer/DMSO mixture to provide fluoroscopic visualization. Upon contact with blood (or body fluids) the solvent (DMSO) rapidly diffuses away causing in-situ precipitation of a soft radiopaque polymeric embolus.

The Onyx Liquid Embolic System (LES) was initially used in clinical feasibility studies at the University of California Los Angeles Medical Center, in Mexico City and in Europe. The Onyx LES has received CE marking and is commercially available in Europe, Australia, Canada, and South America.

Onyx is compositionally similar to the embolization agent, Enteryx, which is sold as the Enteryx Procedure Kit by Enteric Medical Technologies, Inc. Enteryx, as approved by FDA in April, 2003, is indicated for endoscopic injection into the region of the lower esophageal sphincter for the treatment of gastroesophageal reflux disease (GERD) symptoms in patients responding to and requiring daily pharmacological therapy with proton pump inhibitors.

The sponsor has conducted an extensive array of mechanical, chemical, biocompatibility and in vivo effectiveness preclinical evaluations of the product. This review is focused primarily on the biocompatibility and animal effectiveness evaluations. The sponsor has conducted the standard biocompatibility assessments which included 1 year implantation studies, genotoxicity evaluations and carcinogenicity determinations using the rasH2 transgenic mouse model. In addition, the sponsor evaluated the following:

- ?? the effect of injecting the material into the cerebromedullary cistern of the rabbit
- ?? the potential for the material, specifically the DMSO component, to cause angiototoxicity in a swine model with follow-up evaluations at 10 and 28 days
- ?? the embolization effectiveness of the material in the swine rete mirabile model
- ?? the embolization effectiveness of the material in canine and swine surgically-created aneurysm models

The sponsor has also provided a limited histopathologic assessment of Onyx-embolized human tissue and a report comparing the MRI/CT image analyses of n-BCA and Onyx embolized human brain AVMs.

Dimethyl sulfoxide is considered a drug. The only approved use of DMSO in humans is for interstitial cystitis as a 50% solution (RIMSO®). Consult review was requested from colleagues at the Center for Drug Evaluation and Research and their review is included. As noted in the drug review, repeat infusion animal evaluations were not conducted. This issue will be discussed as a question to the panel. The question in draft form is presented here:

Preclinical animal evaluations have shown that the rate and amount of DMSO can cause vasospasm and vascular wall damage. Patients undergoing staged embolization procedures for Cerebral Arteriovenous Malformations will be exposed repeatedly to the potential for DMSO-mediated vessel damage. Do you believe additional animal evaluation should be conducted to more completely assess for repeat-DMSO vessel wall exposure and potential adverse effects? Do you have any recommendations regarding the amount of DMSO a patient should be exposed to over a 24 hour period or the length of time between embolization procedures?

This issue will be discussed further in the second mail-out. Additional preclinical information has been requested from the sponsor and this will be discussed in the preclinical section of the second mail-out as well.

In conclusion, the sponsor has conducted a thorough preclinical assessment of their catheter-based delivery system, device biocompatibility and device proof of concept in animal models. Additional information regarding the repeat injection issue and the sponsor's responses to the issues unanswered to date will be forwarded to you within the next two weeks.

Review:

Device description

Onyx® Liquid Embolization System (LES)

Onyx® 18, Model 105-7100-060

Onyx® 34, Model 105-7100-060

Onyx is a mixture of ethylene vinyl alcohol copolymer (EVOH) dissolved in dimethyl sulfoxide (DMSO). Micronized tantalum powder is suspended in the liquid polymer/DMSO mixture to provide fluoroscopic visualization. The Onyx material is delivered in a liquid phase through a micro catheter to the target lesion under fluoroscopic control. Upon contact with blood (or body fluids) the solvent (DMSO) rapidly diffuses away causing in-situ precipitation of a soft radiopaque polymeric embolus. The sponsor is marketing two viscosities – Onyx 18 and Onyx 34 for use in arteriovenous malformations in which the depth of penetration is important. The formulations are designated 18 or 34 based upon their respective viscosities, i.e., 18 and 34 centistokes, respectively.

Nomenclature

MTI has licensed the Onyx LES technology to Genyx Medical, Inc. under the trade name “Uryx” for treatment of female urinary incontinence, and Enteric Medical, Inc. under the trade name “Enteryx” for treatment of gastro-esophageal reflux disease. MTI, Genyx and Enteric have participated in joint biocompatibility and safety studies for the Onyx material.

<u>Current Product Name</u>	<u>Synonymous Name #1</u>	<u>Synonymous Name #2</u>
Onyx-18	Embolyx-6% or Onyx-6%	Embolyx E-6%
Onyx-34	Embolyx-8% or Onyx-8%	Embolyx E-8%
Uryx	Embolyx-8% or Onyx-8%	N.A.
Enteryx	Embolyx-8% or Onyx-8%	N.A.

The Onyx LES kit contains the following:

- a. one vial (1.5 mL) of Onyx (18 or 34)
- b. one vial of DMSO (1.5 mL)
- c. 3 DMSO compatible syringes (1 mL)

The Onyx material requires use of compatible delivery devices to assure patient safety and effective performance of the embolic material. The instructions for use provide instructions for preparation and use of recommended syringes and delivery catheters. The following ancillary devices are identified in the instructions for use:

- a. MTI UltraFlow™ Micro Catheter (K980104, K010004, K024118)
- b. MTI Rebar™ Micro Catheter (K993672, K001966)
- c. Onyx Syringe (K991225)

The indications for use for the devices recommended in the labeling do not conflict with the manner in which they are used in conjunction with the embolization agent.

Device components

The Onyx material is manufactured from 3 components:

- ?? Dimethyl Sulfoxide
- ?? Ethylene vinyl alcohol copolymer
- ?? Tantalum

The DMSO is used to dissolve the EVOH pellets and the tantalum is used for achieving radiopacity of the final product. The material mix ratio will determine the performance attributes of the Onyx solution; i.e., the viscosity/flow properties and degree of visualization when implanted in the vasculature. Two configurations of Onyx are proposed within this application: Onyx 34 has a greater amount of EVOH in

solution producing a higher viscosity liquid than the Onyx 18. The “18” and “34” designations represent the approximate viscosity of the liquid material. Onyx-18 (6% EVOH) has an approximate viscosity of 18 cSt whereas Onyx-34 (8% EVOH) has an approximate viscosity of 34 cSt at 40° C.

Onyx manufacturing is a batch process (vol. 2, pg. vi)

<u>Part</u>	<u>DMSO</u>	<u>EVOH</u>	<u>Tantalum</u>	<u>Mixed batch size</u>
Onyx-18 (6%)	880.8 g	48 g	264 g	450 vials
Onyx-34 (8%)	880.8 g	64 g	264 g	450 vials

Preclinical test evaluations

Mechanical and Chemical testing

The sponsor uses a number of names to represent the same formulations. The nomenclature is repeated here for reference:

<u>Current Product Name</u>	<u>Synonymous Name #1</u>	<u>Synonymous Name #2</u>
Onyx-18	Embolyx-6% or Onyx-6%	Embolyx E-6%
Onyx-34	Embolyx-8% or Onyx-8%	Embolyx E-8%
Uryx	Embolyx-8% or Onyx-8%	N.A.
Enteryx	Embolyx-8% or Onyx-8%	N.A.

Many of the experiments were done with the material identified as Embolyx 8%. The Embolyx 8% formulation is Onyx 8% and is the formulation of the highest viscosity used in the clinical study. Both formulations of Onyx under review for the treatment of arteriovenous malformations contain 0.33% tantalum. The approved, Cordis Neurovascular cyanoacrylate product (also indicated for the treatment of arteriovenous malformations) is recommended to contain tantalum at a 0.5:1 ratio (w/v), tantalum to cyanoacrylate.

Tests

The sponsor conducted the following investigations:

- ?? Minimum mixing time for Embolyx/Onyx vials using the Vortex Genie 2 Mixer (volume 5)
- ?? Onyx vial mixer study
- ?? Onyx solidification test
- ?? Embolyx 8% mechanical properties post precipitation
- ?? Embolyx 8% solidification time
- ?? Onyx HD 2500 tantalum concentration increase – feasibility
- ?? Design verification 1.5F en-route micro-catheter
- ?? Design verification 1.5F en-route micro-catheter min/max extended testing test protocol
- ?? Design verification, 1.5F UltraFlow micro-catheter Onyx plug and push testing
- ?? Comprehensive Onyx testing summary for the Rebar Series Catheters

- ?? Design verification 1.5F UltraFlow w/optimized distal tubing (P/N 30542A) and optimized coating
- ?? 1.5F UltraFlow HPC and AVM embolic agents compatibility test report
- ?? UltraFlow 1.5F and Flowrider Plus 1.5F comparative comprehensive Onyx testing
- ?? Rebar-10 Micro catheter design verification
- ?? 0.0165" ID Rebar micro catheter design verification
- ?? Titan micro catheter design verification test protocol (hub and introducer luer)
- ?? Design verification 1 mL long stroke syringe

The studies established the correct time to mix the solution and established product physical chemistry specifications. In addition, empiric evidence regarding the influence of tantalum concentration was obtained. Testing of the catheters included many mechanically-based determinations and also investigated the chemical compatibility of the catheters with DMSO. The catheters were assessed in standard biocompatibility tests and their performance was assessed in animal models.

Embolyx compatibility with aneurysm metal coils

The purpose of the study was to determine if the Onyx material was compatible with metal aneurysm coils that might be used in conjunction for embolization of aneurysms but also in cases of high flow AVMs. The sponsor asserts the following:

- ?? The platinum, platinum alloy-based coils do not form soluble metal cations in the human body's aqueous setting (physiologic saline). Stable cations would be necessary to interact with the ethylene vinyl alcohol polymer.
- ?? DMSO has no ionizing capability in aqueous solutions (human physiologic aqueous system) – ionization is necessary to dissolve metal and form metal cations.
- ?? The tantalum metal and metal oxides are stable to most conditions and solutions. Freshly prepared tantalum metal oxide is chemically reactive to hydrofluoric acid. The tantalum used is not a fresh precipitate and hydrofluoric acid will not be encountered in the human physiologic system.

I confirmed the inert chemical character of tantalum by reviewing the text, *Basic Inorganic Chemistry by Cotton and Wilkinson*. Tantalum oxides are only successfully chemically attacked and altered by hydrofluoric acid.

Onyx in vitro coil compatibility study test protocol

The purpose of the study was to determine how the two Onyx formulations (18 and 34) may interact, chemically, with standard metal occlusion coils. Various coils were used to embolize a simulated vessel in conjunction with Onyx. The coils were soaked in DMSO for periods of time up to 60 minutes and the extracts were analyzed for leachates via HPLC.

Results: The two Onyx formulations occluded the vessels as assisted by the occlusion coils without distal migration of the Onyx material. The sponsor states that examination of the DMSO extract from several

coils using HPLC demonstrated an “insignificant” amount of substance was leached from the coil. **The chromatograms were not provided and these are necessary for an independent determination of what insignificant means. In addition, the use of Onyx with coils that may have surface coatings which could be dissolved by DMSO should be discussed in the labeling. This information was requested and is currently under review.**

DMSO and Histoacryl compatibility study test protocol PR99-084, Rev. A

The purpose of the study was to ascertain Onyx compatibility with solidified Histoacryl/Lipiodol mixture.

The compatibility was evaluated for chemical as well as functional interactions. The Histoacryl/Lipiodol mixture was allowed to solidify and then the mixture was exposed to DMSO. Control samples of DMSO alone or unsolidified Histoacryl/Lipiodol were included in the test paradigm.

Protocol deviation: The HPLC testing was performed on a pure Histoacryl mixture and not one mixed with 50% Lipiodol oil.

Results: HPLC analyses did not reveal any differences in peaks or areas under the chromatograms with respect to control. **However, no chromatograms were provided for an independent assessment – these will be requested from the sponsor. This information has been requested and is currently under review.** Functionally, no migration of the histoacryl polymerized cast was observed and no Onyx material was observed to “ooze” through the Histoacryl cast. As a result of these findings the sponsor intends to remove the contraindication statement regarding use of Onyx with cyanoacrylate-based polymeric embolic agents.

If after review of the original chromatograms I find that the sponsor’s interpretation is accurate, I will agree that the contraindication statement can be removed.

In vitro evaluation of the effect of radiosurgery on Embolyx E

The purpose of the study was to determine the effect of stereotactic radiation on the biocompatibility and physical integrity of the material.

Radiation is known to create free radicals in the irradiated polymer materials. These free radicals generally cause either an increase in cross-linking or chain cleavage of polymers. Additionally, chemical by products may be released as a result of the interaction of the radiation energy and the polymer. The sponsor identified 3 questions regarding the potential effect radiation might have on the material:

- ?? Has there been a change in the material, so that the material no longer is biocompatible?
- ?? Is there a degradation of the embolic material so that material may fail or fragment? Has the molecular weight distribution of the polymer changed?
- ?? Is there a degradation of the embolic material after irradiation with time at body temperature?

To address biocompatibility, the sponsor conducted cytotoxicity, hemolysis, pyrogenicity and acute

systemic toxicity evaluations. To determine the effect of radiation on the chemistry or physical chemistry of the polymer, the sponsor conducted gel permeation chromatography and infrared absorption spectroscopy analyses. The material was exposed to 30 Gray of radiation at a distance of 94 cm. Acute, 1 year and 2 year determinations were conducted.

Results: The sponsor asserts that there was no evidence of cellular or systemic toxicity. No additional peaks were found and the size/breadth of the peaks were similar, and therefore deemed identical, using IR spectral analysis. Changes in molecular weight determinations as detected by gel permeation chromatography were within the prescribed acceptance criterion of less than a 20% change. **However, no spectra or chromatograms were provided for an independent assessment. This information has been requested and is currently under review.**

Conclusions: the sponsor notes that a radiation dose of 30 Gray is a high dose relative to any in vivo clinical usage and therefore the lack of an effect on the material indicates that concerns regarding radiation-induced damage to the polymer, and subsequent untoward clinical effects, should be allayed.

Biocompatibility Studies

The sponsor has provided biocompatibility studies using Onyx as it is implanted in the patient. The sponsor conducted the following tests which had passing results (unless noted):

?? Cytotoxicity – Embolyx, 8% Tantalum

?? Cytotoxicity – DMSO (tested at 92%)

?? Sensitization – Embolyx, 8% with Tantalum

?? Intracutaneous reactivity - Embolyx, 8% with Tantalum

?? Acute systemic toxicity – Uryx Embolyx, 8% with Tantalum Pass, with comment

The mice showed a staggering gait and were lethargic immediately post-injection, followed by a staggering gait out to 15 minutes. The animals recovered and gained weight and so passed the USP requirement of the test. The sponsor believes that the DMSO may have contributed to the animals' responses.

?? Subacute toxicity (14 day, I.V.) - Embolyx, 8% with Tantalum Pass with comment

The animals receiving injections of the test material had tremors, twitches, spasms and/or a staggering gait during or immediately after dosing for a few seconds on most or all of the 14 days of dosing. Piloerection was also observed. At AM/PM observations, all animals appeared normal. The sponsor believes that this indicates that the reactions observed during and immediately after dosing were transient and were most probably due to the DMSO component of the extract being administered I.V. and not due to a toxicity related to the polymer. Mean white blood cell counts for the test animals were significantly lower than the control but the sponsor indicated that in 2 of the test animals' samples, blood clots were noticed and believed to be responsible for the abnormally low value. Looking at the other blood cell and blood parameter determinations, I believe the sponsor's interpretation. Volume 6

?? Implantation (7 day, muscle) - Embolyx, 8% with Tantalum

?? Implantation (1 year, rabbit) - Embolyx, 8% with and w/o Tantalum

Intramuscular injection sites were examined microscopically and other tissues were examined microscopically to look for the possibility of systemic migration of test article. Severity grading of histopathologic diagnoses was done on a scale of 1-4.

30 days: There were histopathologic differences in the appearance of the injection sites containing material with and without tantalum, microscopically. The inflammatory response observed due to material containing tantalum was less severe than that seen due to material lacking tantalum. The implantation sites contained phagocytic cells, occasional infiltrates of lymphocytes, heterophils and also contained spotty fibrosis. Multinucleated giant cells were observed in both implantation sites and were observed to be degenerating in the sites containing material without tantalum. The control implantation sites were unremarkable.

90 days: The inflammatory response seen in areas of test article administration consisted of a mild (+2) localized foreign body reaction that was of similar type whether the material contained tantalum or not. The inflammatory reaction was characterized by a predominance of macrophages and multinucleate giant cells with fewer numbers of lymphocytes and plasma cells. Occasional multinucleate giant cells were observed and patchy fibrosis and mineralization of skeletal muscle bundles was observed.

Conclusion at 90 days: The investigator asserts that the lack of histomorphologic differences in the nature and severity of the inflammatory response observed with material containing or not containing tantalum indicates that there is "little meaningful difference in tissues response under the conditions of the study".

181 days: The inflammatory response seen in areas of test article administration was frequently minimal (+1) and occasionally mild (+2) in severity (only material with tantalum was assessed at this time point). Rarely, severity of this reaction was judged to be moderate (+). The inflammatory response was typical of a localized foreign body reaction and was characterized by macrophages and multinucleate giant cells with fewer numbers of lymphocytes and plasma cells.

216 days: The inflammatory response seen in areas of test article administration was frequently minimal (+1) and occasionally mild (+2) in severity (only material with tantalum was assessed at this time point). Unlike the samples evaluated at 181 days, there were no occurrences of moderate (+3) severity of the inflammatory response. The inflammatory response was typical of a localized foreign body reaction and was characterized by macrophages and multinucleate giant cells with fewer numbers of lymphocytes and plasma cells.

362 days: The inflammatory response seen in areas of test article administration was frequently minimal (+1) and occasionally mild (+2) in severity (both materials, i.e., with tantalum and without tantalum were assessed at this time point). The inflammatory responses were typical of a localized foreign body reaction and were characterized by macrophages and multinucleate giant cells with fewer numbers of lymphocytes and plasma cells.

In summary, the observations indicate that the presence of tantalum in the material did not alter the inflammatory response observed to the embolic material. The histophotomicrographs indicate that the material (with or without tantalum) elicits a similar inflammatory response and that over the course of the study i.e., out to 1 year, the response gradually lessens in both cases. The test articles were not observed to migrate from the site of implantation.

?? Genotoxicity (Ames mutagenicity) –Embolyx, 8% with Tantalum

?? Genotoxicity (*In vitro* mammalian cell) - Embolyx, 8% with Tantalum

?? Genotoxicity (Micronucleus) - Embolyx, 8% with Tantalum

?? Carcinogenicity (rasH2 Transgenic mouse) - Embolyx, 8% with Tantalum Pass with comment

Previously reviewed during the investigational phase of the study, this protocol evaluated the liquid embolic material (ethylene vinyl alcohol) with and without tantalum. The device tested contained 8% EVOH dissolved in DMSO containing tantalum (30% w/v)/Volume 7. The test articles were administered as a single subcutaneous injection into the interscapular region of the dorsal surface of the animal.

Animal Studies

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.

The cerebello-medullary cistern is formed by the arachnoid bridging the interval between the medulla oblongata and the inferior surface of the cerebellum and is triangular on sagittal section. Here the arachnoid is separated from the pia mater by wide intervals, which communicate freely with each other and are named subarachnoid cisterns. The space is filled with cerebrospinal fluid and blood vessels of the brain.

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. Nonsubtracted images documented placement of the polymer in the cisterna magna. Animal evaluations were conducted at 2, 4, or 90 days via angiography, and gross and microscopic histopathology. At least 3 sections were trimmed, to include representative sections of the medulla oblongata and cerebellum and were examined by a board-certified veterinary pathologist.

Results

The results and raw data (day 90) of the study were provided. The reviewing pathologist states, “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.” The vasculitis was observed exclusively in the Onyx treated animals and reached its highest incidence in the 6% Onyx group and was of lower incidence in the 25% Onyx group. Onyx polymer was observed in the meninges overlying the medulla oblongata or cerebellum, less frequently observed in the cistern and occasionally found in the cerebellum parenchyma. Another finding unique to Onyx treated animals was a proteinaceous exudates observed on days 2 and 4. Also, there was an increase in the incidence and severity of subacute inflammation in the meninges in Onyx treated animals. The incidence and severity of proteinaceous exudates and subacute inflammation were comparable between the 6 and 25% groups. On day 90 vasculitis and proteinaceous exudates were not observed in the meninges. Onyx was present in the meninges of most brains and was associated with minimal to moderate accumulation of foreign body giant cells and occasional mineralization and/or osseous metaplasia.

“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.” “On day 90, only subarachnoidal changes were observed and consisted of degeneration/necrosis in the medulla in two Onyx treated animals and subarachnoidal gliosis often with neuropile mineralization in 3 Onyx treated rabbits. The distribution of this change in the cerebellum and medulla oblongata 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 is involved in the pathogenesis of this change in the rabbit and that direct toxicity of the Onyx is 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 like saline or blood would be.”

The raw data/observations from day 90 indicate that the vasculitis and proteinaceous exudates were of short duration, i.e., seen at 2 and 4 days but not reported out to 90 days. The inflammatory response observed early, i.e., 2 and 4 days, was severe (3) in 2 of 4 animals and either slight or moderate in the other 2 animals at 90 days. I believe the reviewing pathologist’s interpretation that the necrosis and subarachnoid gliosis observed can be explained by increased intracranial pressure due to the unresorbed EVOH polymer is reasonable. I think the study indicates that the risk of adverse events or complications due to the material escaping the vascular site into brain parenchyma is slight. However, the information could be used for constitution of a warning or precaution on the product label.

Proposed Warning or precaution

Animal experimentation has shown that when Onyx escapes outside the vascular space, as might occur if the vessel wall is compromised, a subacute inflammatory response to the material may occur. Increased intracranial pressure due to unresorbed Onyx material in this space may cause tissue damage.

Study of angiotoxicity of DMSO utilizing the rete mirabile in the swine model test protocol

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. The sponsor chose the swine rete mirabile animal model for the evaluation. Previous work by other investigators had shown that infusion of DMSO could cause “severe, rapidly progressive vasospasm in the distal ascending pharyngeal artery and retial arteries.” “Histological results showed hemorrhage, angioneclerosis and thrombosis.” Further evaluation of DMSO associated vascular toxicity indicated that slower infusion rates minimized angiotoxicity.

The experiment was conducted to address the time of injection of DMSO at two volumes. The amount of the DMSO used to prime the catheter was assumed to be 0.3 mL. 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 grading system was developed for the Thrombolysis in Myocardial Infarction (TIMI) Clinical Trials.

Results

The results indicate that a slow and controlled infusion of DMSO (anhydrous) has no severe or permanent vascular effect in the swine model. The 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. Vasospasm did occur in all animals injected. In 21 of 24 cases the vasospasm showed complete resolution and in the remaining 3 cases minimal residual vasospasm was noted. At fast injections, i.e., above 0.5 mL/min. or greater, gross and microscopic histopathology revealed inflammatory reactions and intimal hyperplasia.

The investigators note that for some types of clinical applications it actually may be desirable to use an embolic agent that elicits a more intense inflammatory reaction, since the affected vessels in such cases are less likely to develop recanalization. This potential enhancement in durability, however, may be counterbalanced by potential increased peritherapeutic morbidity related to innocent bystander histotoxicity of adjacent normal organ tissue.

As noted by the sponsor, repeat injections of DMSO and potential vascular injury was not evaluated in this study. This is a safety concern that should be addressed, as pointed out by CDER consultant reviewers, by panel discussion.

Because the potential for vasospasm and vascular injury is a significant concern, the product label and instructions for use must provide sufficient information for individuals to use the product safely.

Proposed Warning

The infusion rate of Onyx/DMSO (polymer solvent) must be carefully controlled. More rapid infusion of DMSO in animal studies was shown to cause vasospasm and vascular wall damage.

Proposed Panel Question

Preclinical animal evaluations have shown that the rate and amount of DMSO can cause vasospasm and vascular wall damage. These experiments were conducted with a one-time injection of DMSO and short (10 day) and chronic (28 day) follow-up. Patients undergoing staged embolization procedures for Cerebral Arteriovenous Malformations will be exposed repeatedly to the potential for DMSO-mediated vessel damage. Do you believe additional animal evaluation should be conducted to more completely assess for repeat-DMSO vessel wall exposure and potential adverse effects?

Evaluation of Embolyx E8 for Embolization of AVMs Using the Rete Mirabile in the Swine Model

The purpose of the study was to evaluate the use of the device as an embolization agent in the swine rete mirabile. This study was one of the earlier safety and efficacy evaluations of the product.

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.

Embolization protocol: DMSO delivery was maintained at 0.3 mL over 5-10 seconds for catheter priming. Delivery of the material ranged from 0.1-0.6 mL with delivery rates of 5-14 $\mu\text{L}/\text{second}$. The mean Embolyx/Onyx volume and delivery rate was **0.25 mL and 10 $\mu\text{L}/\text{second}$** .

Results: There were no reported incidences of vasospasm during the procedures and all swine recovered without evidence of neurological deterioration or behavior change. There was no reported abnormality or deterioration in swine behavior following embolization or through chronic maintenance periods. There were no embolization related technical problems associated with using the catheters – no reported incidents of catheter occlusion, rupture or adhesion to the embolic mass.

Histology/gross and microscopic

- ?? Gross examination of harvested rete was reported as spongy and easily resected and no significant abnormality, rupture, or hemorrhage was observed.
- ?? Control rete specimens were unremarkable with normal vasculature in all respects
- ?? Acute specimens of retes were grossly unremarkable with no significant abnormalities. The acute specimens showed occlusion of the arteries with embolic material without evidence of endothelial denudation or arterial wall angioneclerosis. There was no evidence of an acute cellular inflammatory response or hemorrhage in the perivascular spaces. Mild focal disruption of the lumen wall with embolic material and a mild inflammatory response was observed in 1/7 specimens.
- ?? In the 3 and 6 month chronic specimen groups retes were occluded by dense aggregates of black particulate material, **and a robust intraluminal foreign body giant cell reaction with**

massive multinucleated cells totally occluding most of the lumina. Surrounding the foreign body giant cells were abundant lymphoplasmacytoid cells. Thrombi, although occlusive and sometimes organizing, did not appear to extend through the vessel walls, i.e., the foreign body giant cell and lymphoplasmacytoid reaction was largely superficial to the internal elastica lamina, although they prominently indented into the elastica in a few areas. **No histological evidence of arterial wall angioneclerosis was identified in these chronic rete specimens.** Focal elastica disruption without angioneclerosis was identified in most specimens.

?? At 12 months, the rete specimens had histological findings substantially equivalent to the 3 and 6 month chronic embolization groups, but exhibited a substantial **decrease** in chronic inflammation in 4/5 specimens. Disruption of the elastica was observed in 4/5 specimens with focal intimal hyperplasia occurring in 2/5 specimens. Non-material thrombi, generally well organized, were present in 4/5 specimens with indications of early calcification in 1/5. Negligible recanalization was observed in 1/5 specimens. Overall, there was no observed eosinophilic activity or hemosiderin/hematoidan present. **The foreign body giant cell response was moderate to heavy in 4/5 specimens. No arterial wall angioneclerosis or extravasation of embolic material was observed in any specimen.**

Conclusions/comments

The authors note that the DMSO and Embolyx/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 technical problems reported. Histopathological results indicated hyperplasia, inflammatory reaction, foreign body giant cells and focal disruption of elastica due to the foreign material. No significant recanalization, hemorrhage or angioneclerosis was reported.

The investigators state that **“additional safety issues relative to the cumulative histotoxicity on local and perivascular tissue may need to be addressed for outcome optimization.”**

With respect to the histopathological changes observed, the authors noted that PVA particles and N-butyl cyanoacrylate glue both have been reported to elicit similar effects. References identified by the sponsor support the assertion that the histologic response observed in this study is not unlike what has been observed previously with other embolic agents. In a study by Germano et al (J Neurosurgery, 1992, 76:607-614) surgical specimens of 66 human cerebral arteriovenous malformations were analyzed to determine the sequence of histopathological events after embolization with poly vinyl alcohol particles. “Poly vinyl alcohol particles indented the endothelium in 69% of cases but were rarely found subendothelially. Clotted blood and fibroblasts were present among the particles and abundant intraluminal mononuclear and polymorphonuclear inflammatory cells were found in all vessels containing PVA particles. Foreign body giant cells appeared 2-14 days after embolization in most cases. Patchy mural angioneclerosis and necrotizing vasculitis was found in 39% of the cases. Recanalized lumina were seen in 18% of PVA-embolized vessels.” Vinters et al (N Engl J Med 1986; 314:477-483) examined 17 intracranial arteriovenous malformations that were resected after treatment by embolization using

isobutyl-2-cyanoacrylate. “In 9 specimens removed 5 days to 16 months after embolization therapy, a series of pathologic changes was seen, including patchy mural angionecrosis (adjacent to the isobutyl cyanoacrylate fragment) up to 6 weeks after embolization, the presence of isobutyl cyanoacrylate in vessel walls and fibromuscular intimal cushions, and the occurrence (after several months) of entirely extravascular isobutyl cyanoacrylate. Occasional parts of recanalized vascular malformations were identified. Isobutyl cyanoacrylate was present within arteriovenous malformations as late as 16 months after embolization although the amount appeared to be diminished. These findings suggest a specific sequence of events in the interaction between isobutyl cyanoacrylate and mural components within the malformations and may explain some important complications of embolization therapy.” The authors also noted that foreign body giant cells, perivascular cuffing by mononuclear inflammatory cells, and widespread necrosis was observed. “Angionecrosis was not observed later than 41 days after embolization but [they] did not have the opportunity to examine a specimen in the critical follow-up period from 41 days to 3.5 months. In addition to necrosis of the channel walls (which was identified by the presence of karyorrhexis of mural nuclei, intense eosinophilia, and polymorphonuclear infiltration throughout the full thickness of the wall layers) necrosis of parenchyma adjacent to embolized channels (with or without an inflammatory response) was observed.”

Commentary by reviewing contributors of the paper regarding the animal study results published in Neurosurgery (1998) by Murayama et al raised 2 concerns:

?? DMSO compatible catheters must be used due to the ability of the solvent to chemically degrade some polymers. The sponsor acknowledged this concern in their development of DMSO compatible catheters designed for use with the embolic agent.

?? The use of this embolic agent may have limitation in cases of AVMs with high-flow arteriovenous fistulae because of the danger of migration of the embolic agent into the venous drainage system. The reviewer notes that the issue is not resolved by the animal study because the swine rete mirabile is close to a plexiform AVM but does not mimic the common clinical scenario of an AVM with a high-flow arteriovenous fistula. Another reviewer states that “because of its lack of adhesiveness, [the embolic agent] may migrate into the venous site in high-flow fistulae, and it may be necessary to combine this agent with other agents, such as coils, buffers, or acrylics, to close the high-flow fistulae and reserve this embolic agent for a nidus type architecture.

Study: Onyx aneurysm system: embolization of experimental aneurysms

The purpose of the study was to evaluate the feasibility of treating intracranial aneurysm by embolization with the subject device. The information obtained in these evaluation, although more directly applicable to treatment of aneurysms, can be extrapolated to the treatment of AVMs and the histopathologic assessment for tissue responses to the material.

Methods: 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 include aneurysm occlusion, parent artery patency, procedural complications, and overall system performance. Sixteen animals in a pivotal series were assessed at 3, 6, or 12 months after treatment. Angiographic assessment of aneurysm fill and arterial patency was obtained prior to animal sacrifice. Fourteen additional aneurysms were treated with GDC coils and used for histopathological control comparison to Onyx treated animals at the 3 and 6 month chronic follow-up evaluations.

Aneurysm embolization was performed using a “flow arrest” technique in which a balloon occlusion catheter placed in the parent artery with the balloon bridging the aneurysm neck effectively isolates the aneurysm from the parent artery flow dynamics. The temporary interruption of blood flow and stasis within the aneurysm sac permits delivery and precipitation of the Onyx material from a pre-positioned delivery catheter. **Delivery of Onyx was staged with alternating periods of balloon deflation to re-establish blood flow through the parent vessel.** Angiographic assessment of aneurysm occlusion was performed at the completion of the embolization procedure and again immediately prior to animal sacrifice at designated implant periods. Observations were recorded relative to aneurysm fill, neck remnant, protrusion or migration of embolic material, and vasospasm or thrombotic events associated with the treatment. Animals were closely monitored daily for up to 12 weeks after treatment for indications of physical impairment or abnormal behavior. At the conclusion of each study period, aneurysms were excised and preserved for gross and microscopic histologic analysis. Aneurysm morphology was characterized with detailed observations of aneurysm fill, tissue remodeling at neck, protrusion or migration of embolic material, and inflammatory response to the embolic materials. The brain and rete mirabile of 3 swine were removed and submitted for analysis of the effect of DMSO, and signs of brain infarct, hemorrhage or softening of brain tissue.

Results: In the sponsor’s narrative they state that, “overall physician assessment rated the Onyx system performance as “acceptable” to “excellent” when compared to GDC experience and performance.” “Delivery of Onyx within the aneurysm sac was controllable and well tolerated by the animals with no significant technical or procedural incidents that would suggest a compromise of safety in a clinical setting. Pre-sacrifice angiography at 3, 6, and 12 months following embolization confirmed parent artery patency and sustained angiographic obliteration of the aneurysm with no incidence of recanalization. Aneurysm histopathology specimens at 3, 6, and 12 month time periods showed complete healing of the aneurysm neck with acceptable tissue response comparable to GDC treated aneurysms with inflammation diminishing to mild focal collections of lymphocytes and giant cells in 12 month chronic specimens. There was no evidence of aneurysm rupture or wall erosion seen in any specimen. Healthy neointimal tissue remodeling with variably mature endothelial cell growth was observed across the aneurysm neck in continuity with the parent artery lumen in all Onyx treated aneurysms of the pivotal study group.”

Developmental Study Series Results – detailed

A number of complications were observed in the developmental research series, i.e., those animals embolized using various modifications of the delivery system and embolization protocol. Physician assessment of the procedure and treatment outcome rated 16/21 as “acceptable” to “excellent” when

compared to embolization with GDC coils. Three of 21 were rated “terrible” due to procedure or device related complications. Summary embolization results are provided in the table below:

Acute angiographic aneurysm assessment

Occlusion = 95%	11
Occlusion = 90-95%	3
Incomplete fill < 90%	4
Not recorded	3

Three animal deaths occurred in the developmental series; 2 in recovery and 1 during treatment. Two animals had transient visual impairment. One animal, with a 3 day visual impairment following treatment, had migration of Onyx reported and external carotid artery occlusion at 14 day follow-up angiography. Brain pathology showed significant fibrin emboli consistent with the thrombotic arterial occlusion observed during treatment. No Onyx material was detected. A second animal, with a 2 day visual impairment following treatment, had vasospasm reported during the treatment and transient parent artery occlusion at completion. Histopathology showed the parent artery attenuated with marked denudation and loss of smooth muscle cells attributed to a balloon dilatation procedure to resolve the vasospasm. Parent artery stenosis or complete occlusion occurred in 8 animals. Restriction of the parent artery with Onyx and thrombus occurred in 4 animals. Complete thrombotic occlusion occurred in 3 animals and a transient arterial occlusion in 1 animal. Thirteen occurrences of Onyx protrusion were observed and 4 incidents of Onyx migration in the parent artery. Nine of the 13 protrusions were unremarkable. Resistance to detachment of the delivery catheter from the aneurysm at completion of embolization occurred in 4 procedures and adhesion of the Onyx to the delivery catheter in 3 procedures. A modified version of the FlowRider micro catheter incorporation of a low profile marker band and siliconized distal tip coating minimized further incidents.

Pivotal Study Series – detailed

Complications again were observed, if at a lower incidence than was observed in the developmental series animals. Physician assessment of the procedure and treatment outcome rated 15 of 16 embolizations as “acceptable” to “excellent” when compared to GDC treatment experience. Physician assessment of GDC treatment rated 14 of 14 as “good”. The percent of aneurysm fill with Onyx and GDC is provided:

Summary Embolization results

<u>Aneurysm occlusion</u>	<u>Onyx</u>	<u>GDC</u>
100%	8	8
= 95%	5*	0
90-95%	2	0
Incomplete	0	2
Not available	-	4

* one aneurysm is counted twice since it was 95%

The incidence of Onyx leakage into the parent vessel was significantly reduced in the pivotal series following implementation of device and procedure refinements. Two incidents were reported. Four of 14 aneurysms treated with GDC coils had coil protrusion angiographically observed in the parent artery at completion of treatment. Arterial vasospasm and clot formation were observed in both Onyx and GDC treated animals. The rate of occurrence in the Onyx group exceeded that reported for the GDC treated group. One animal death in the Onyx group occurred although necropsy attributed death to respiratory distress caused by regurgitation and intubation trauma. One Onyx treated animal experienced a seizure in recovery that resolved with no additional complications. Two Onyx treated animals had transient parent artery occlusion angiographically observed at completion of treatment. One of the 2 had some arterial vasospasm associated with catheter detachment from the aneurysm following embolization and one had experienced intra-procedure vasospasm and post-procedure clot formation. Both occlusions resolved with no further sequelae.

Histopathologic observations

Histopathologic examination of aneurysms in the pivotal series was performed to correlate angiographic assessment with actual morphologic presentation of the aneurysm, i.e., to verify isolation of the aneurysm from the parent artery flow dynamics and to evaluate the acute and chronic tissue response to the Onyx material. In addition, the brains and rete mirabile of 3 swine were studied to observe for tissue reaction or significant sequelae distal to the aneurysm site.

The Onyx precipitate within the aneurysm sac was generally a conformal mass characterized by cohesive peripheral laminations and a central homogenous core. The precipitated masses remained non-adherent within the aneurysm site. Chronic time point specimens were characterized by active and sometimes obliterative fibrosis at 6 and 12 months. The aneurysm sac and inner surfaces were characterized by mild to moderate and occasionally severe, inflammation with palisading histiocytes rimming the polymer cast. At 12 months, 2 of 3 specimens had a mild inflammatory reaction limited to focal collections of lymphocytes in the aneurysm wall with occasional giant cells lining the Onyx mass. One of the 12 month specimens had marked chronic lympho-histiocytic inflammatory response and numerous giant cells in the aneurysm wall. Masses of necrotic acute inflammatory cells were observed in hollow spaces and invaginations of the Onyx mass. The inflammatory response was suggestive of delayed healing possibly due to compromise of sterility at the time of treatment. Inflammation was frequently associated with sutures in most specimens (i.e., sutures were used to help surgically create the aneurysm), but rarely extended to the parent vessel or neointimal growth across the aneurysm neck. The aneurysm necks were typically filled with Onyx precipitate and either covered with fresh thrombus in acute specimens or a variably organized thrombus and fibro-muscular neointimal tissue isolating the sac from the parent artery in chronic specimens. Progressive to complete development of endothelial tissue over the fibro-muscular membrane was observed in chronic specimens at 21 through 88 days. Neointimal tissue remodeling readily developed over the surface of the Onyx in the aneurysm neck of all specimens examined at 3, 6 and 12 month chronic periods. Neointimal tissue thickness reported for 3 specimens at 3 months was 0.7-1.08 mm – a thickness comparable to the parent artery wall thickness. The mean neointimal tissue thickness for 3, 6 and 12 month specimens combined was 1.1 mm and

ranges from 0.48 to 1.93 mm thick.

Some endothelial denudation of the parent arteries was observed in acute specimens and occasionally in chronic specimens adjacent and/or contralateral to the arterial anastomosis and sutures. This observation is most likely related to the surgical trauma caused during creation of the aneurysm. Neointimal tissue remodeling at the aneurysm neck of chronic specimens was observed smooth and in continuity with the parent vessel. Occasional mild to moderate parent vessel inflammation was observed with rare fibrosis and intimal hyperplasia. Occasional neutrophilic infiltrate of parent artery intima and internal elastic layer adjacent to the aneurysm neck was observed originating from the anastomoses and sutures. The rete mirabile and brains of 3 animals who had died in recovery, or had visual impairment or parent vessel occlusion were sectioned and processed for histopathology analyses. The rete and brains were generally unremarkable with minimal to mild mononuclear cell infiltrates observed. Nine aneurysms treated with GDC coils were examined histopathologically for comparison to the Onyx treated animals. All specimens showed complete healing of the aneurysm neck with well-organized intimal growth consisting of smooth muscle cells in a proteoglycan-rich matrix. Intimal growth over the necks was essentially equal in both the 3 month and 6 month groups with a mean thickness of 0.92 mm that ranged from 0.48 to 1.93 mm thick. Two specimens had parent artery compromise of 50% and 95% from a thrombus. There was moderate to extensive chronic lympho-histiocytic infiltration of the sac and occasional multi-nucleated giant cells along the surface of the coils. Healing and thrombus organization within the aneurysm sac had progressed from granular tissue with chronic inflammatory infiltration seen at 3 months to more organized, highly vascularized fibrous tissue formation with diminished inflammation at 6 months. Specimens showed either focal erosion of the aneurysm wall or were extremely attenuated. An aneurysm sac from a 3 month specimen appeared to have ruptured with coils protruding from the sac. Endothelial tissue growth across the neck was seen in all 3 month specimens and of 3 of 4 specimens at 6 months.

Reviewer's interpretation: I believe the information supports the sponsor's assertion that aneurysms treated with Onyx exhibited an "acceptable tissue response" in that the response does not appear to be worse than, or significantly different from what is observed with GDC coils. This study, including the developmental series of experiments, I believe, mirrors what has been seen, or would be seen histologically, in the human clinical evaluation of the product. The material elicits an acute inflammatory response that evolves into a chronic response which includes the infiltration of lympho-histiocytic cells. Foreign body giant cells are observed as usually are with implanted medical devices. The inflammatory response does not appear to be worse than what is seen with GDC coils which are legally marketed embolization agents. Although the study reported here was presented by the sponsor in support of an aneurysm indication for use, the information is relevant to the use of the product on arteriovenous malformations, and especially arteriovenous malformations that do not undergo surgical excision. I also believe this study somewhat addresses the "repeat" DMSO vasculature exposure concern. The material was layered on as would be done during embolization of an AVM or an aneurysm, and so, vascular necrosis or vasospasm due to repeat instillation of DMSO has been assessed in this model. What has not been answered by this study is whether patients undergoing staged embolization procedures in which the procedures are separated in time are at greater risk for vascular complications

due to repeat exposure to DMSO.

Histopathology study: evaluations of cerebral arteriovenous malformations embolized with Embolyx liquid embolic

To assess Onyx for potential chronic histotoxic effects, 7 BAVMs embolized with Onyx were surgically excised and submitted for evaluation to a board certified histopathologist. 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.

The tissue evaluated was obtained from patients in either the Mexico City Embolyx Pilot Study or the International Brain Arteriovenous Malformation Clinical study.

Results: BAVM (brain AVM) sizes ranged from 2.3 to 93.65 cm³ (mean size 35 cm³). Prior to surgery, 1 of 7 patients received a single embolization treatment, 2 of 7 received 2 treatments, 1 of 7 received 3 treatments and 3 of 7 received 4 treatments. The timing between embolization and surgery ranged from 1 week to 19 months while all patient had pre-surgical embolization periods of at least 3 months, i.e., no one had one embolization procedure and then within 1 week went to surgery whereas some patients may have had multiple embolization procedures with the last one being 1 week prior to surgery.

With specific note to the concern regarding repeat exposure to DMSO

Two patients had 4 and 5 feeder vessels respectively embolized during their initial embolization treatment. The volume of DMSO delivered was recorded at 1.2 and 1.05 cc, and the volume of Embolyx was 0.25 and 2.77 cc, respectively. These patients continued with additional treatments, receiving a total of 2.05 and 1.90 cc of DMSO and 1.35 and 4.08 cc of Embolyx respectively prior to surgical excision of their AVMs. **“The volume (and exposure) of DMSO and Embolyx seemed to be well tolerated by the vasculature and the histopathology for these specimens appears unremarkable.”** The report shows favorable results (albeit limited), with no indication of vascular necrosis, rupture or extravasation of the Embolyx material. In 5 of 6 AVMs receiving multiple embolization treatments, progressive reduction of AVM size was reported with each embolization and there were no reported ischemic or hemorrhagic complications resulting from untoward migration or abrupt occlusion of an AVM nidus.

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

A review of CT, MRI and flat film skull x-rays obtained from patients whose BAVMs were treated with Onyx or n-BCA was performed for MTI by a central reader to determine if any direct neurotoxicity due to Onyx can be detected in the grain post-embolization. A total of 54 patients were studied in the Onyx group and 19 in the n-BCA group (total = 73). The central reader was blinded as to treatment. All MRI and CT studies were evaluated for the presence of absence of gliosis, encephalomalacia, edema, leptomeningeal or parenchymal enhancement and hemorrhage. These parameters were pre-defined based on specific imaging characteristics.

Results: The average time post-embolization for all imaging studies was 23 months, with a range of 9 to 50 months. Forty-one patients of the 73 had imaging findings that required an assessment as to whether the finding was due to the device. Twelve of the 19 n-BCA patients had imaging changes that were due to: concurrent neurosurgical resection of the AVM, changes in the brain related to neurosurgery, or due to the natural history of the AVM. Twenty-nine of 54 patients in the Onyx groups demonstrated imaging findings post-embolization that were not present pre-embolization. The reader (Director, Clinical Image Processing Service for UCLA Department of Radiological Sciences) asserts that “in all cases the etiology of the post-embolization findings was found to be due to events unrelated to the presence of Onyx.” The findings were believed to be due to radiosurgery, surgical resection of the AVM and the natural history of the AVM. The images were not provided in the report found in amendment 3 to MAF1071. An FDA radiologist reviewed the images and their review of the images did not disagree with the sponsor’s interpretation.

This review is not finalized. Additional information has been requested and review comments will be provided in the second mail-out.