

SUMMARY MINUTES

MEETING OF THE NEUROLOGICAL DEVICES ADVISORY PANEL

OPEN SESSION

August 5, 2003

**Gaithersburg Holiday Inn
Gaithersburg, MD**

**Neurological Devices Advisory Panel Meeting
August 5, 2003**

Open Session

Attendees

Chairperson

Robert W. Hurst, M.D.
Hospital of the University of Pennsylvania

Executive Secretary

Janet L. Scudiero, M.S.

Voting Members

Kyra J. Becker, M.D.
University of Washington School of
Medicine

Fernando G. Diaz, M.D., Ph.D.
Detroit Medical Center

Jonas H. Ellenberg, Ph.D.
Westat

Stephen J. Haines, M.D.
Medical University of South Carolina

Steve G. Massaquoi, M.D., Ph.D.
Massachusetts Institute of Technology

Consultants

Mary E. Jensen, M.D.
University of Virginia Health Sciences
Center

Thomas L. Kurt, M.D., M.P.H.
University of Texas Southwestern

Fong Y. Tsai, M.D.
University of California, Irvine

Consumer Representative

Crissy E. Wells, R.T., M.B.A., M.H.S.A.
Western Regional Community Clinical
Oncology Program

Industry Representative

Andrew K. Balo
DexCom, Inc.

Food and Drug Administration

Celia Witten, M.D., Ph.D.
Director, Division of General, Restorative,
and Neurological Devices

Stephen P. Rhodes, M.S.
Chief, General and Plastic Surgery Devices
Branch

Peter L. Hudson, Ph.D.
Preclinical Reviewer, Plastic and
Reconstructive Surgery Devices Branch

Ann Costello, Ph.D., M.D.M
Clinical Reviewer, Plastic and
Reconstructive Surgery Devices Branch

Judy Chen, M.S.
Statistical Reviewer, Office of Surveillance
and Biostatistics

CALL TO ORDER

Panel Executive Secretary Janet Scudiero, M.S., called the meeting to order at 10:31 a.m. She noted that Mary E. Jensen, M.D., Thomas L. Kurt, M.D., M.P.H., and Fong Y. Tsai, M.D., had been appointed to temporary voting status for the duration of the meeting. She then read the conflict of interest statement; full waivers had been granted to Drs. Hurst and Jensen, who reported current or past interests in firms at issue but in matters not related to the day's agenda. Ms. Scudiero noted that the panel meeting scheduled for September 24 and 25 was cancelled; the next meeting is tentatively scheduled for December 8 and 9. Finally, she stated this is the last meeting for Drs. Hurst and Massaquoi, and she thanked them for their service to the panel.

Celia Witten, M.D., Ph.D., Director, Division of General, Restorative, and Neurological Devices (DGRND), stated that the Agency appreciates the time and energy that Drs. Massaquoi and Hurst have put forth in their service to the panel.

Panel Chair Robert W. Hurst, M.D., noted that the purpose of the meeting is for the panel to make recommendations to FDA on the approvability of PMA 030004, the Onyx® Liquid Embolic System (LES). He asked the panel members to introduce themselves and noted that the voting members present constitute a quorum.

PANEL UPDATE

Stephen P. Rhodes, M.S., Chief, General and Plastic Surgery Devices Branch (PRSB), updated the panel on the Agency's activities since the November 2000 panel meeting. On August 9, 2002, the Agency approved an HDE for Guidant Corporation's Neurolink System, a stent indicated for the treatment of patients with recurrent intracranial stroke attributable to atherosclerotic disease refractory to medical therapy in intracranial vessels ranging from 2.5 to

4.5 mm in diameter with greater than 50 percent stenosis. On September 11, 2002, the Agency approved an HDE for Smart Therapeutics' Neuroform Microdelivery Stent System, which is intended for use with embolic coils for the treatment of wide neck, intracranial, saccular aneurysms arising from a parent vessel with a diameter of 2.0 to 4.5 mm. On April 15, 2003, the Agency approved an HDE for Medtronic's Activa Dystonia Therapy Kit, indicated for unilateral or bilateral stimulation in the management of chronic, intractable primary dystonia in patients age 7 or older.

Two regulatory actions that the panel recommended in previous meetings are undergoing review: the Classification Final Rule for Human Dura Mater and the Reclassification Proposed Rule for Neurological and Cardiovascular Embolization Devices.

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No comments were made.

SPONSOR PRESENTATION

Amy Walters, Vice President, Quality Assurance, Clinical, and Regulatory Affairs, Microtherapeutics, Inc. (MTI), noted that the company develops, manufactures, and markets minimally invasive medical devices for the diagnosis and treatment of vascular diseases. She reviewed the statement of intended use for the Onyx® LES: "an artificial embolization device intended for use in the treatment of brain arteriovenous malformations (AVMs), when embolization is indicated to minimize blood loss or to reduce the brain AVM size prior to surgery." Ms. Walters summarized the history of the PMA and listed the sponsor's consultants attending the meeting.

Bill Patterson, Ph.D., Senior Director, Research and Development, MTI, stated that the Onyx® LES is a premixed, radioopaque, injectable embolic fluid; the device is based on the physical property of polymer solubility. It has three components: ethylene vinyl alcohol copolymer (EVOH), which is dissolved in dimethyl sulfoxide (DMSO), and tantalum which is added for radiopacity. Polymer precipitation occurs upon contact with aqueous solution. The device was first used for vascular embolization in 1996. The device received marketing approval in Europe for brain AVMs in 1999. FDA has approved the same device known as Enteryx and licensed to another company for the treatment of gastroesophageal reflux disease in February 2003. The Onyx® LES is available in two viscosities: 18 (6 percent) and 34 (8 percent). The device is packaged as a kit consisting of Onyx®, DMSO, and DMSO-compatible syringes and microcatheters. A small volume of DMSO is used to prime the catheter to prevent premature precipitation.

Dr. Patterson then summarized the preclinical testing. In mechanical and chemical testing, the sponsor has characterized the Onyx® LES as a liquid and as a solid. All ISO 10993 tests recommended for medical devices having long-term blood contact were conducted. The device did not meet requirements for USP 7-day muscle implant evaluation because implantation resulted in an acute tissue response greater than that seen with controls, but the inflammation subsides over time. Neurovascular animal models found that large volumes of DMSO at high flow rates cause angiototoxicity; however, no angiototoxicity was found when small doses of DMSO were injected at a slow rate.

Responding to FDA's concerns, Dr. Patterson noted that a histopathology study of seven specimens from human subjects implanted with Onyx® LES was conducted. The study found that repeated exposure to DMSO in human clinical use showed no vascular necrosis in the

histopathology, nor any evidence of rupture, extravasation, fragmentation, or distal migration of the material. DMSO is absorbed readily and distributed throughout total body water; it is metabolized to dimethylsulfone (DMSO₂), which is excreted in urine, and dimethylsulfide (DMS), which is exhaled. Excretion is complete in about 2 weeks. DMSO and its metabolites have low acute toxicity at the levels used in the Onyx® LES. The dose of DMSO delivered with Onyx® LES is similar to that of other devices. He concluded stating that in vitro, animal, and human studies, provide reasonable assurance that the Onyx® LES is safe for brain AVMs.

Gary Duckwiler, M.D., UCLA Medical Center, Principal Investigator, presented the sponsor's clinical data. After providing information on the incidence and natural history of brain AVMs, he listed some of the drawbacks of current treatment methods. Endovascular embolization reduces brain AVM size and bloodflow prior to surgery, enables treatment of high-flow fistulae, enables access to and exclusion of surgically difficult feeders, and permits staged embolization for large brain AVMs. Treatment challenges include the heterogeneity of BAVMs; a low prevalence rate, making it difficult to enroll patients; and variable presentations.

Dr. Duckwiler reviewed the advantages and disadvantages of existing embolic agents, which consist of particulates, liquids, or coils. The Onyx® LES has superior clinical utility because it is nonthrombogenic and nonadherent; is preformulated; has consistent viscosity; and is a radiopaque liquid. It is administered through slow, controlled injection and allows contrast injection during treatment.

The PMA is based on data from a noninferiority trial comparing the Onyx® LES and the Cordis Trufill® device, a device using n-butyl-cyanoacrylate (n-BCA) in achieving at least 50 percent brain AVM volume reduction. The multicenter, randomized study enrolled presurgical

brain AVM patients at 20 sites. Clinical events were adjudicated by an independent physician medical monitor; the data safety monitoring board was chaired by Donald W. Larsen, M.D. The primary efficacy endpoint was technical success, defined as angiographic reduction in brain AVM volume of 50 percent or greater. Secondary endpoints were surgical blood loss and resection time. Safety endpoints were system-, treatment-, surgery-, and disease-related adverse events. If a patient did not go to surgery, or if the brain AVM was only partially resected, adverse events were collected at discharge and at 3 and 12 months.

Dr. Duckwiler listed the study's inclusion and exclusion criteria and patient demographic data. The patients in the two groups were comparable in their presenting symptoms and baseline neurological indices, although more n-BCA patients presented with neurologic deficit. Dr. Duckwiler reviewed other data from the study, including total mean volume of DMSO delivery across embolization stages, duration of Onyx® injection, and use of adjunctive devices.

The intent-to-treat analysis yielded 43 patients (79.6 percent) categorized as successes in the n-BCA group and 41 patients (89.1 percent) categorized as successes in the Onyx® LES group. No significant differences were found in patient demographics. Patients in the Onyx® LES group had a significantly higher success rate than those in the control group. No significant differences were found between the groups in the secondary endpoints. The two groups were comparable in their rates of serious adverse events; however, three patients in the Onyx® LES group and none in the n-BCA group died. The deaths were not associated with the Onyx® LES procedure but with surgery in response to stroke and hemorrhage. Eight instances of difficulty removing the delivery catheter occurred in Onyx® LES patients, only one of which was associated with a serious adverse event. He concluded that the data support a reasonable assurance of the safety and efficacy of the Onyx® LES.

G. Lee Pride, Jr., M.D., Clinical Investigator, discussed his experience with the Onyx® LES. His site had a positive experience with the agent. Its embolic characteristics were favorable, and surgeons believed that they had greater control than with the Trufill n-BCA device. No difficulty with catheter removal was experienced. The Onyx® LES material is more malleable than glue and can be moved out of the way, making resection of AVM easier.

Ms. Walters described the physician training program, which includes a didactic session, a hands-on in vitro workshop, case review, and case observation by an experienced user. The hands-on workshop will simulate overpressurization during training so that physicians can experience the tactile feedback occurring during the embolization procedure.

Panel Questions for Sponsor

Panel members raised questions concerning the histopathology of tissue around the AVM and the Onyx® LES material, particularly in the patients who died. They had many questions concerning the effects of the device on blood vessels and the possible contribution of the embolic agent to bleeding. They noted that the method of injection, free flow or wedge, could affect the material's effect on vessels. Panel members also asked clarifying questions about catheter compatibility with DMSO and the sponsor's training program. Sponsor representatives responded to the questions to the panel's satisfaction.

It was suggested that a pressure sensor to guard against catheter rupture could be a useful addition to the device. Panel members also requested data from the European experience with the device, which the sponsor was not able to provide.

FDA PRESENTATION

Peter L. Hudson, Ph.D., PRSB, presented the Agency's preclinical review. He reviewed device and its components and noted that although Onyx® LES is intended to be a presurgical tool, not all patients ultimately have surgical resection. Therefore, it is important to consider that the device might be permanently implanted. Dr. Hudson summarized the biocompatibility tests that had been conducted. The device passed the hemolysis test, increased clotting time by 18 percent, and activated c3a complement. Although DMSO can cause hemolysis and be angiotoxic, the dose in the Onyx® LES is 200-fold lower than the DMSO LD₅₀.

Dr. Hudson reviewed the data on DMSO angiotoxicity in animal models; he noted that with uncontrolled injection, the chemical caused severe vasospasm and other problems. At lower injection rates and doses, it can still cause a robust foreign body response, which decreases over time. In an aneurysm model, the tissue response to Onyx® LES was found to be equivalent to that with GDC coils.

In humans, DMSO has produced no evidence of vascular necrosis or rupture. MRI evaluation found that in roughly half of patients, pre- and postoperative image changes were consistent with radiation, surgical resection, or natural history of the brain AVM itself. Additional preclinical testing was conducted on the polymer, including analysis of the effects of radiation and possible interaction with platinum coils and cyanoacrylate liquid embolic agents. No breakdown from radiation occurred, and no degradative byproducts or chemical reactions were found.

Although the extensive biocompatibility assessments appear to indicate relative safety, the Agency has several concerns. The rate of DMSO infusion is critically important. In addition, some patients will be undergoing several embolization procedures before surgery, and it is

unclear what the effects of multiple doses over time are, particularly if patients do not have surgical excision.

Ann H. Costello, Ph.D., D.M.D., PRSB, provided FDA's clinical review. She reviewed the indications for use and noted that the objective of the pivotal trial was to demonstrate that the Onyx® LES was no worse than n-BCA in terms of efficacy within a 20 percent specified clinical tolerance. She briefly reviewed the patient inclusion criteria, accountability data, demographics, presenting symptoms, and pretreatment assessments. The data are based on 102 patients. The groups were similar in terms of pretreatment assessments except for body mass index, which was significantly higher in the Onyx® LES group than in the n-BCA group. A statistically significantly greater number of patients in the n-BCA group had a history of aneurysm. Most patients had some type of neurological deficits and/or symptoms.

Dr. Costello noted that Onyx® comes in two formulations: Onyx® 18 and 34. The sponsor has provided specific instructions on when to use Onyx® 18 and 34, and provided details on Onyx® LES and n-BCA use in the study. Coils were used significantly more often in the n-BCA group.

Onyx® and n-BCA are equivalent in attaining at least a 50 percent reduction in brain AVM size. Postprocedure neurological assessment was similar as well. Dr. Costello presented tables listing all adverse events. Three patients died and two had strokes in the Onyx® LES group. The third Onyx® LES death had just recently been reported; the panel only received data on two deaths. More patients in the Onyx® LES group had hydrocephalus, reported discomfort, and had access site bleeding. There were 10 reports of delivery catheter removal difficulty and more reports of poor penetration and visualization in the Onyx® LES group. Physician ratings of

device performance differed somewhat between the two groups. FDA analysis of the frequency of certain cranial complications found that the numbers were higher than the sponsor reported, but they were nevertheless comparable across the two groups.

In addition, just a few days prior to the meeting, the sponsor reported new data on catheter removal difficulties. The Agency had not had time to review the additional data.

Judy Chen, M.S., Office of Surveillance and Biostatistics, provided FDA's statistical review. She reviewed the study design and objectives, then described the three analysis populations: FDA's intent to treat (ITT), the sponsor's ITT, and the sponsor's "conservative ITT." The problem with the sponsor's ITT analysis is that the original randomization is not preserved and stratification is ignored. Comparing the Onyx® LES group to the n-BCA group, the odds ratio for success is 1.55 with a 1-sided 95 percent confidence limit of 0.68. Assuming homogeneity of treatment differences across centers, Onyx® LES is not inferior to n-BCA in the proportion of patients rated as successes. However, because of large variability, no statistical conclusions can be reached on the secondary endpoints of blood loss or resection time.

PANEL PRESENTATIONS

Thomas L. Kurt, M.D., M.P.H., presented the panel preclinical review. He stated that he wanted to be assured that due to the storage conditions of up to 55 degrees Centigrade, carbon disulfide production would not occur. He then noted that the Onyx® LES material EVOH copolymer is not toxic as some related chemicals are. Other pertinent considerations are that dosage in brain may not be equivalent to doses elsewhere in body; interactions with certain medications, such as hydantoin and benzodiazepines, are possible; and drift to other vascular locations, such as the pituitary and basal ganglia, could occur. None of the Onyx® LES

components are listed in the National Toxicology Program's *10th Report on Carcinogens*. Other concerns include storage stability, long-term breakdown of EVOH, and the sterilization process for the catheters. If they are to be resterilized, it is important to ensure that no leaching of residual ethylene oxide, a gas sterilant, occurs when EVOH is run through the catheter.

A histological examination of the brain of the third death in the Onyx® LES group should be conducted. The sponsor should evaluate the potential for human vasculitis by reporting the microscopic pathologic findings in the dead patients and in any subsequent deaths during patient follow-up. It should also check immunoglobulin E levels serially in a small number of patients (approximately ten) and check plasma hemoglobin and haptoglobin levels in a similar subset of ten patients. Finally, the sponsor should explain the statement on its website that "Onyx® LES lacks adhesive properties" in view of the stuck catheters in the clinical trial and this clarification should be included in the labeling.

Mary E. Jensen, M.D., presented the panel's clinical review. The study was generally good, but it had several weaknesses, including a small number of patients; loss of patients due to late screen failure and loss to follow-up; and sites with differential enrollment, resulting in interoperator variation. The number of patients analyzed on different indexes made it difficult to compare across groups. Dr. Jensen noted a lack of pathological data outside the resected area and on normal parts of brain. A reality of treating AVMs is that not every patient has subsequent resection. Long-term safety data are needed for nonresected patients. In addition, the sponsor provided incomplete explanations for some of the technical issues, such as poor visualization and the inability to withdraw catheters. One concern is the effect Onyx® LES might have in patients previously treated with alcohol, a question the animal testing did not examine.

Serious complications could occur in the hands of inadequately trained clinicians. Training should include hands-on experience that includes use of fluoroscopy. Because of the extremely slow injection rate, it is important for clinicians to understand that it will take a minute or more to see the material on a fluoroscope. Surgeons should not be exempt from training just because of their experience with n-BCA. It is good that the sponsor is incorporating potential complications into the training. The sponsor needs to be more specific about the timing of repeat embolizations; with n-BCA, it can be done every other day. The trainees should use both Onyx® LES formulations. Clinicians need to understand what the appropriate flow state is with regard to choice of material. Proctoring is crucial.

Jonas H. Ellenberg, Ph.D., provided the panel statistical review. He reviewed the study design, calling the approach “extremely interesting.” He asked why a 50 percent reduction was considered the primary endpoint. Setting the bar that low might skew the study in favor of noninferiority. Eighty percent might have been more appropriate. Page 97 of the panel submission showed data for only 60 percent of subjects; what happened to the others?

The goal of the procedure is to prepare a patient for surgery. What is the absolute postembolism AVM size that allows for postsurgical success? In addition, preembolization AVM size and sites should have been included in the analysis. Were the goals reached without accounting for imbalances in randomization, adjusting for subtle differences? The univariate analysis on p. 96 of the panel pack, which indicates that size is not a predictor of outcome, may be too crude an assessment to reject a more subtle association. Why did the sponsor not adjust for covariates in its secondary analysis? It is important to be sure that all potential confounders are considered. Reduction in AVM size is not only a surrogate for whether the patient is

adequately prepped for surgery, but also for whether outcome is better using one approach or other. Long-term follow up should be considered.

Regarding the secondary efficacy endpoints, the power for detecting differences in estimated blood loss in the two groups is very low, perhaps 10 percent. The result is not dispositive, so no conclusions can be drawn. The same is true for resection time. Dr. Ellenberg concurred with Ms. Chen's conclusions concerning safety.

OPEN COMMITTEE DISCUSSION

Panel members expressed concerns over the pivotal study methodology and endpoints, including the impact different centers may have had in the pivotal study findings; compatibility of microcatheters with DMSO; the toxicology issues Dr. Kurt raised earlier; the frequency of vasospasm and hydrocephaly in the Onyx® LES group; whether Onyx® LES treatment predisposes patients to late hemorrhagic complications; the effects of future radiosurgery on Onyx® LES-treated patients; and catheter rupture and the problem of Onyx® LES catheters sticking. Many panel members expressed concerns about device safety.

PANEL QUESTIONS

- 1. Do you believe that the data in the PMA adequately support the safety of repeated exposure to DMSO as required in the proposed use of the product? If not, please provide suggestions on the additional preclinical studies that you believe are needed to demonstrate the safety of the repeated exposure to DMSO.**

The panel concurred that the data adequately support the safety of repeated exposure to DMSO. Data on patients treated in Europe should be examined. Effects of possible interactions with prior or subsequent use of alcohol or radiosurgery in treatment are unclear. Postmarket follow-up is warranted.

2. Please discuss whether the data in the PMA provide a reasonable assurance of safety.

Most panel members believed that the sponsor had demonstrated safety. However, several panel members noted an important difference in serious adverse events between the two groups. All the deaths were in the Onyx® LES group. The study is not sufficiently powerful to assess even a doubling of complication rates. Long-term data would be helpful in answering the panel's concerns.

3. Please discuss whether the data in the PMA provide a reasonable assurance of effectiveness.

The panel concurred that the data provide reasonable assurance of effectiveness, but many questions remain concerning the pivotal trial, such as whether the bar is sufficient at 50 percent and whether long-term follow-up is warranted. Training is also an issue.

4. Please comment on the sponsor's proposed training plan and whether you believe it is adequate to help ensure proper device use.

Some panel members believed that training information was insufficient to answer the question, particularly the reported poor penetration and visualization of the device. The panel concurred that training is critically important. It should include a mandatory hands-on component, proctoring, monitoring of the program's effectiveness, and mandatory supervision by someone who can remove the catheter should it become stuck. Even for experienced clinicians, using Onyx® LES is not as simple as those with n-BCA experience might think.

5. Do you believe a long-term follow-up study for patients not undergoing surgical resection of their AVM should be conducted as a condition of approval?

The panel concurred that a long-term follow-up study on such patients should be mandatory. Long-term follow-up data are needed on surgical patients as well. Studies should include

angiography and an imaging component. Follow-up duration for nonsurgical and radiosurgery patients should be 3 to 5 years; 1 year is adequate for patients who have surgery. Follow-up can end when a patient has complete obliteration of the AVM.

OPEN PUBLIC HEARING

No comments were made.

SPONSOR SUMMATION

MTI representatives provided additional information in response to some of the concerns that FDA representatives and the panel raised. They reiterated that no difference in the overall complication rate was found between the n-BCA group and the Onyx® LES group. Median blood loss was comparable, and DMSO was not associated with greater rates of adverse events. None of the reports of poor visualization were associated with clinical sequelae. The Onyx® LES rate of flow is quite different from that of n-BCA, and some of the difficulty surgeons experienced was associated with the slow administration of the Onyx® LES. The catheter currently used with Onyx® LES is an Ultraflow catheter, which is not associated with ruptures.

The sponsor clarified several issues concerning DMSO. The device is implemented via intraarterial administration, using slow injection of small doses to minimize irritation; the priming DMSO dose is about 2 drops. DMSO is completely eliminated after 14 days. In multivariate regression analysis, DMSO was not associated with complications. All MRI and CT follow-ups found no abnormalities that could be attributed to DMSO. The sponsor referred the panel to its white paper on DMSO.

Sponsor representatives reiterated that the company is asking for approval for a presurgical indication; the device is not intended for use with radiation therapy.

PANEL VOTE

Executive Secretary Scudiero read the panel voting options. The panel voted six to one (with one abstention) that the device was approvable with the following conditions:

1. The sponsor should investigate the possibility of angiototoxicity and vasculitis histopathologically in the brains of deceased patients and in biopsies of proximate tissue in surgically excised Onyx® LES in a subset of patients, approximately ten.
2. The sponsor should investigate the possibility of hemolysis in a subset of patients, approximately 10, by checking plasma hemoglobin and haptoglobin postinjection.
3. The sponsor should revise the labeling to point out that Onyx®-related catheters may become stuck.
4. Postmarketing follow-up of the patients in the pivotal study should occur for three to five years for nonresected patients and for one year for those who were resected.
5. The training program must include a hands-on component that incorporates observing material under fluoroscope, use of both Onyx® LES viscosities, and at least one proctored case. If the proctored case fails, the trainee must repeat the training until successful.
6. The sponsor should make a concerted effort to collect and report to FDA all European Onyx® LES data that exists.
7. The labeling should include a warning that during the pivotal study, all fatalities occurred in the Onyx® LES group; although there is no specific indication whether this might be related to the device, the possible role of the device is unknown.

POLL

When asked to explain the rationale for their votes, many panel members stressed that although the sponsor had provided data demonstrating reasonable assurance of safety and efficacy, their recommendation for approval was cautious. FDA should seriously consider rescinding approval if the panel's recommendations are not followed. The panel members who voted no or abstained stated that they were not convinced that the sponsor had demonstrated safety and that the study design had too many problems.

ADJOURNMENT

Dr. Witten thanked the participants on behalf of FDA, and Dr. Hurst adjourned the meeting at 5:02 p.m.

I certify that I attended this meeting of the Neurological Devices Advisory Panel Meeting on August 5, 2003, and that these minutes accurately reflect what transpired.

Janet L. Scudiero, M.S.
Executive Secretary

I approve the minutes of this meeting
as recorded in this summary.

Robert W. Hurst, M.D.
Chairperson

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