資料(3)-2-(1)-2 の和訳

Nuroform Microdelivery Stent System – H020002

第一部 - 承認書

第二部 - 安全性と予想される利点の概要 [Word]

第三部 - 患者表示

その他の消費者情報

資料(3)-2-(1)-3

前出資料(3)-2-(1)-2 のパート 1 をクリックしたもの
CDRH からの認証時の文書

原文（英文）とその和訳

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Ms. Theresa E. Brandner
Director of Regulatory Affairs
SMART Therapeutics, Inc.
2551 Merced Street
San Leandro, California 94577

SEP 1 1 2002

Re: H020002
Neuroform™ Microdelivery Stent System
Filed: April 2, 2002
Amended: April 22, April 25, April 29, May 20, and July 5, 2002

Dear Ms. Brandner:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your humanitarian device exemption (HDE) application for the Neuroform™ Microdelivery Stent System. This device is indicated for use with embolic coils for the treatment of wide neck, intracranial, saccular aneurysms arising from a parent vessel with a diameter of ≥2mm and ≤4.5mm that are not amenable to treatment with surgical clipping. Wide neck aneurysms are defined as having a neck of ≥4mm or a dome-to-neck ratio of <2. CDRH is pleased to inform you that your HDE is approved subject to the enclosed "Conditions of Approval." You may begin commercial distribution of the device after you have submitted an amendment to this HDE with copies of the approved labeling in final printed form.

The sale, distribution, and use of this device are limited to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. In addition, in order to ensure the safe use of the device, FDA has further restricted the device within the meaning of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

FDA wishes to remind you that failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

CDRH will notify the public of its decision to approve your HDE by making available a summary of the safety and probable benefit of the device upon which the approval was based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/ode/hdeinfo.html. Written requests for this information can also be made

to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the HDE number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this HDE submission with copies of all approved labeling in final printed form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will not routinely be reviewed by FDA staff when HDE applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at http://www.fda.gov/cdrh/pmat/pilotpmat.html for further details.

Any information to be submitted to FDA regarding this HDE should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above HDE number to facilitate processing:

Document Mail Center (HFZ-401)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Ms. Samie Allen at (301) 594-3090, x139.

Sincerely yours,

Daniel G. Schultz, M.D.
Director
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

資料(3)-2-(1)-3 の和訳

健康および福祉サービス部　　米国公衆衛生局

2002 年 9 月 11 日

ＸＸＸＸＸＸ
Director of Regulatory Affairs
SMART Therapeutics, Inc.

件名：H020002
Neuroform™ Microdelivery Stent System
申請日：2002 年 4 月 2 日
修正日：2002 年 4 月 22 日、4 月 25 日、4 月 29 日、5 月 20 日および 7 月 5 日

ＸＸＸＸＸＸ:

FDA の CDRH は Neuroform™ Microdelivery Stent System についての貴社の HDE 申請の審査を完了した。この機器は、直径が 2mm～4.5mm の親血管に生じた、外科的クリップの処置が適用できない、付け根の大きい、頭蓋内、小嚢性動脈瘤の治療用に塞栓コイルと共に使用するためのものであると示されている。付け根の大きい動脈瘤とは、付け根が 4mm 以上のものまたは球体部と付け根の比率が 2 以上のものと定義される。CDRH は、同封の「承認条件」に従って貴社の HDE を承認したことを知らせる。貴社は、最終的に印刷されたフォームの承認ラベルのコピーを付した HDE の補正書を提出後に本機器を商業的に流通させることができる。

本機器の販売、流通、および使用は、連邦食品、医薬品および化粧品法（本法）のセクション 520(e)の趣旨の範囲内で本法セクション 515(d)(1)(B)(ii)の権限のもとで 21 CFR 801.109 に従った治療の使用に制限される。更に、本機器の安全使用を確実にするため、FDA は、販売、流通、および使用が本法セクション 502(q)および(r)を違反してはならないという範囲において、本法セクション 515(d)(1)(B)(ii)の権限のもとに本法セクション 520(e)の趣旨の範囲内に本機器を限定した。

FDA は承認条件を貴社が順守しない場合には、本承認命令が無効になることを貴社に指摘しておく。この条件を順守しない機器の商業的流通は本法の違反となる。

CDRH は、承認の基礎である機器の安全性と予想される利点の概略の閲覧させることにより、貴社の HDE の承認決定を一般に通知する。この情報は http://www.fda.gov/cdrh/ode/hdeinfo.html にある FDA CDRH のホームページ上で見られ

る。この情報は the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852 に書面にて請求することもできる。書面による請求には、HDE の番号または記録番号の記載が必要。本法セクション 515(g)に基づき、この情報がインターネット上に掲載された日から 30 日以内に、利害関係者はヒアリングあるいは独立の諮問委員会による審査のいずれかによる行政審査の機会を求めることにより、この決定の審査を請求することができる。

貴社は、可及的速やかに、かつ貴社の機器の商業的流通の前に、最終的な印刷の形式による全ての承認ラベルと共に、HDE 提出の補正を提出しなければならないことに留意すること。私どもの業務革新努力の一環として、機器評価局 (Office of Device Evaluation) は、最終的な印刷ラベルの審査に関する新たなプロセスを試行中である。HDE 申請人が最終的に印刷されたラベルの提出と共に、最終的に印刷されたラベルがドラフトの形式で承認されたラベルと同一である旨述べた送り状も提出した場合、ラベリングは FDA が通常の審査を行わない。最終的に印刷されたラベルが同一でない場合、最終的なラベルのドラフトからの変更を強調し補正書の中で説明しなければならない。更に詳しくは、http://www.fda.gov/cdrh/pmat/pilotpmat.html の最終的に印刷されたラベルの審査に関する CDRH の試行(CDRH Pilot for Review of Final Printed Labeling)を参照すること。

この HDE に関して FDA に提出する情報は、別途指定のない限り、下記住所宛に 3 部提出し、手続を容易にする為に上記の HDE 番号を付すべきものとする。

Document Mail Center (HFz-401)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Tockville, Maryland 20850

本承認命令に関して質問がある場合は、(301)594-3090, x139 の Ms. Samie Allen にご連絡されたい。

敬具
Daniel G. Schults, M.D.
Director
Office of Device Evaluation
Center for Devices and Radiological Health

資料(3)-2-(1)-4

前出資料(3)-2-(1)-2 のパート２をクリックしたもの
安全性と予想される利点の概要

原文（英文）とその和訳

SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name:	Intravascular Stent
Device Trade Name:	Neuroform Microdelivery Stent System
Applicant's Name and Address:	SMART Therapeutics, Inc. 2551 Merced St. San Leandro, CA 94577 USA
Humanitarian Device Exemption Number:	H020002
Date of Humanitarian Use Device Designation:	August 14, 2000
Date of Panel Recommendation:	Not applicable
Date of Good Manufacturing Practices Inspection:	August 12, 2002
Date of Notice to the Applicant:	September 11, 2002

II. INDICATIONS FOR USE

The Neuroform™ Microdelivery Stent System 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 ≥2mm and ≤4.5mm that are not amenable to treatment with surgical clipping. Wide neck aneurysms are defined as having a neck of ≥4mm or a dome-to-neck ratio of <2.

III. CONTRAINDICATION

The Neuroform™ Microdelivery Stent System is contraindicated for use in patients in whom antiplatelet and/or anticoagulation therapy is contraindicated.

IV. WARNINGS AND PRECAUTIONS

See the *Warnings* and *Precautions* sections in the final labeling (*Instructions for Use*) for the Neuroform™ Microdelivery Stent System.

V. DEVICE DESCRIPTION

The Neuroform™ Microdelivery Stent System consists of a self-expanding, neurovascular, nitinol Stent and Delivery System intended for use with embolic coils. The Stent is deployed onto healthy vascular tissue. Once the Stent is deployed, embolic coils are delivered through the struts of the Stent. The Stent is used to retain embolic coils within the aneurysm. The Neuroform™ Microdelivery Stent System is provided sterile to the user (EO sterilized).

The Neuroform™ Microdelivery Stent System consists of the following components:

- 1 Neuroform Microdelivery Stent
- 1 - 3F Microdelivery Catheter
- 1 - 2F Stabilizer Catheter
- 1 Peelable Sheath
- 2 Rotating Hemostasis Valves

A more detailed description of each of the five components of the Neuroform™ Microdelivery Stent System follows:

Neuroform Microdelivery Stent - The Stent has a tubular mesh (zig-zag struts) design. There are 4, 6, or 8 distinct sections along the length of the Stent, depending on the Stent length. Sections are joined by 2 interconnecting struts. It is made from nitinol. There are 8 radiopaque markerbands, 4 per end, which are secured to tabs on the Stent. The Stent is available in five diameters (2.5mm to 4.5mm) and three lengths (10mm, 15mm, and 20mm).

3F Microdelivery Catheter - The 3F Microdelivery Catheter is used to deliver the Stent to the treatment site within the patient's parent artery. The 3F Microdelivery Catheter is a single lumen, over-the-wire microcatheter. The material composition of the catheter shaft changes over the length of it to create three distinct stiffness regions: proximal, middle, and distal. The proximal end has a strain relief and standard, female luer fitting. The 3F Microdelivery Catheter is hydrophilically coated. The 3F Microdelivery Catheter is provided sterile with the Stent and Peelable Sheath preloaded. The shaft has an overall nominal working length of 135cm.

2F Stabilizer Catheter - The 2F Stabilizer Catheter is used within the 3F Microdelivery Catheter to hold the Stent stationary and enable deployment. The 2F Stabilizer Catheter contains a proximal hub, polymer tubing, and a radiopaque markerband at the distal tip. The 2F Stabilizer Catheter is provided sterile and has an overall nominal working length of 162cm.

Peelable Sheath - The Peelable Sheath is used to facilitate guidewire backloading into the 3F Microdelivery Catheter and through the preloaded Stent. The Peelable Sheath is comprised of a single piece of notched tubing (i.e., slit through its length). The Peelable Sheath is provided to the user pre-inserted through the preloaded Stent with a portion extending from the distal tip of the 3F Microdelivery Catheter. After backloading the guidewire and prior to insertion of the Neuroform™ Microdelivery Stent System into the patient, the Peelable Sheath is removed from the 3F Microdelivery Catheter and peeled from the guidewire by the physician.

Rotating Hemostatic Valves - The Rotating Hemostatic Valves (RHVs) are used to provide reliable hemostasis while allowing continuous heparinized saline flush through both the 2F Stabilizer Catheter and 3F Microdelivery Catheter. Each RHV has a standard Y-shaped configuration with (1) one standard male connector and (2) one standard Tuoghy-Borst connector with an adjustable hemostasis port. One RHV is included in each sterile catheter pouch. Prior to clinical use, the RHV is secured to the proximal end of the 3F Microdelivery Catheter and 2F Stabilizer Catheter.

Table 1 summarizes the sizing guidelines for the Neuroform™ Microdelivery Stent System.

Table 1: Recommended Sizing Guidelines

Labeled Stent Diameter (mm)	Labeled Stent Length (mm)	Self-Expanded Stent Diameter (mm)	Recommended Vessel Diameter[2] (mm)	Useable 3F Microdelivery Catheter Length	Useable 2F Stabilizer Catheter Length	Maximum Guidewire Diameter	Minimum Guide Catheter Inner Diameter
2.5	10	3.0	>2.0 and ≤ 2.5	131 cm	161 cm	0.014 in	0.050 in
2.5	15	3.0	>2.0 and ≤ 2.5				
2.5	20	3.0	>2.0 and ≤ 2.5				
3.0	10	3.5	>2.5 and ≤ 3.0				
3.0	15	3.5	>2.5 and ≤ 3.0				
3.0	20	3.5	>2.5 and ≤ 3.0				
3.5	10	4.0	>3.0 and ≤ 3.5				
3.5	15	4.0	>3.0 and ≤ 3.5				
3.5	20	4.0	>3.0 and ≤ 3.5				
4.0	10	4.5	>3.5 and ≤ 4.0				
4.0	15	4.5	>3.5 and ≤ 4.0				
4.0	20	4.5	>3.5 and ≤ 4.0				
4.5	10	5.0	>4.0 and ≤ 4.5				
4.5	15	5.0	>4.0 and ≤ 4.5				
4.5	20	5.0	>4.0 and ≤ 4.5				

[1]Select a Stent length that is at least 8mm longer than the aneurysm neck to maintain a minimum of 4mm on each side of the aneurysm neck along the parent vessel.

[2]Select a Stent diameter based on the sizing recommendations in Table 1 and based on the larger vessel diameter (proximal or distal reference vessel diameter).

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Wide neck aneurysms are often untreatable surgically or endovascularly with the devices that are currently approved for neurovascular use, which are clipping and coiling.

Clipping involves surgically placing an implantable clip over the neck of the aneurysm, thereby isolating the aneurysm from the circulation. This technique involves precise placement of the clip and requires access to the vessel from the outside to completely capture the neck of the aneurysm. However, some wide neck aneurysms in vessels deep within the brain are not amendable to being treated by open brain surgery.

Coiling involves endovascular placement of embolization coils into the aneurysm sac in order to exclude the aneurysm from the circulation. The advantage is that the coils can be placed from within the vessel. Limitations to coiling wide neck aneurysms include (1) aneurysm neck instability that could lead to coil protrusion and/or embolization and (2) achieving and maintaining sufficiently dense coil packing of the aneurysm to permanently exclude blood flow.

If left untreated or inadequately treated, the wide neck aneurysms are at risk of rupture, resulting in a high risk of patient morbidity and mortality.

VII. MARKETING HISTORY

The Neuroform™ Microdelivery Stent System has not yet been marketed in any country.

VIII. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential Adverse Effects

The potential adverse events listed below, as well as others, may be associated with the use of the Neuroform™ Microdelivery Stent System or with the procedure:

Aneurysm perforation or rupture
Cerebral ischemia
Coagulopathy
Coil herniation through Stent into parent vessel
Confusion
Death
Embolic stroke
Hematoma, pain, and/or infection at access site
Incomplete aneurysm occlusion
Intimal dissection
Intracerebral/intracranial hemorrhage
Peripheral thromboembolic events
Post-procedure bleeding
Pseudoaneurysm formation
Renal failure
Stent migration
Stent misplacement
Stent occlusion
Vasospasm
Vessel perforation
Vessel thrombosis

Observed Adverse Effects

Tables 2 and 3 identify the adverse events observed in the clinical study conducted with the Neuroform™ Microdelivery Stent System. Twenty-nine patients were implanted with the Stent. The tables include all adverse events through 6 months. Of the 29 patients implanted with the Stent, 17 patients had 1 or more adverse events and 5 had 1 or more serious adverse events. There were 12 serious adverse events and 21 other adverse events, all of which occurred prior to or by the time of discharge. None occurred between discharge and the 6-month timepoint. Nine patients had 1 adverse event, 4 patients had 2 adverse events, 1 patient had 3 adverse events, 2 patients had 4 adverse events, and 1 patient had 5 adverse events.

Table 2 summarizes the patient rates for observed serious adverse events. Table 3 summarizes the patient rates for all other observed adverse events.

Table 2: Serious Device or Procedure-Related Adverse Events

Serious Adverse Event[1]	n (%)
Death[2]	1 (3.4%)
Aneurysm Perforation[2,3]	2 (6.9%)
Arterial Perforation[4]	1 (3.4%)
Subarachnoid/Interventricular Hemorrhage[2,3]	2 (6.9%)
Thromboembolic Stroke[4]	1 (3.4%)
Intracerebral Hematoma[4]	1 (3.4%)
Left Hemiparesis[4]	1 (3.4%)
Intraparenchymal Bleeding[3]	1 (3.4%)
Retroperitoneal Hematoma[5]	1 (3.4%)
Confusion[6]	1 (3.4%)

[1]Five patients had these 12 serious adverse events. The "n" reflects the number of occurrences of that adverse event. The % is based on 29 patients who were assessed before or at discharge when all adverse events occurred.

[2]One patient had 3 serious adverse events. There was perforation of the aneurysm dome with the micro guidewire during the initial catheterization of the aneurysm resulting in subarachnoid/interventricular hemorrhage and death. Death was due to complications from

aneurysm perforation leading to bleeding and pre-existing hepatitis and management of anticoagulation therapy.
[3]One patient had 3 serious adverse events. There was perforation of the aneurysm with the microcatheter during coil placement resulting in subarachnoid hemorrhage and subsequent intraparenchymal bleeding (from the ventricular drainage line).
[4]One patient had 4 serious adverse events. Arterial perforation occurred with the tip of the exchange length guidewire prior to Stent insertion, resulting in an intracerebral hematoma. This patient also had a thromboembolic stroke that led to left hemiparesis.
[5]One patient had a retroperitoneal hematoma.
[6]One patient had confusion. Confusion was categorized by the protocol as a non-serious adverse event; however, it was determined by the clinical study investigator to be a serious adverse event because the patient required a prolonged hospital stay.

Table 3: Other Device or Procedure-Related Adverse Events

Other Adverse Event[1]	n (%)
Right Hemiparesis	1 (3.4%)
Embolic Event[2]	4 (13.8%)
Vasospasm[3]	5 (17.2%)
Intimal Dissection[4]	1 (3.4%)
Seizure[5]	1 (3.4%)
Access Site Hematoma[6]	2 (6.9%)
Liver Failure	1 (3.4%)
Vomiting	1 (3.4%)
Headache	3 (10.3%)
Fever of Unknown Origin	1 (3.4%)
Urinary Tract Infection	1 (3.4%)

[1]Fifteen patients had these 21 adverse events. The "n" reflects the number of occurrences of that adverse event. The % is based on 29 patients who are accounted for and were assessed before or at discharge when all adverse events occurred.
[2]Includes embolic ischemic lesion, small embolic lesion, asymptomatic microemboli to brain detected by MRI, and left prolonged reversible ischemic neurological deficit (PRIND). All embolic events resulted in mild neurological deficits. Three completely resolved, and 1 patient was discharged to a rehabilitation facility.
[3]Includes 4 mild and 1 moderate case. All completely resolved.
[4]Occurred during placement of the guide catheter in the cervical internal carotid prior to Stent placement, not in the portion of the vessel treated with the device.
[5]One patient with a history of epilepsy experienced a seizure with no permanent sequelae while in the hospital.
[6]Includes 1 mild and 1 moderate case. Both resolved.

IX. SUMMARY OF PRECLINICAL STUDIES

Biocompatibility Testing

Biocompatibility testing of the Stent alone and combined the Neuroform™ Microdelivery Stent System was shown to be acceptable by the following tests that were performed in accordance with the provisions of ISO 10993-1 and Good Laboratory Practice (GLP) Regulations, 21 CFR 58:

- Acute Intracutaneous Reactivity (Irritation)
- Acute Systemic Toxicity
- Sensitization (Guinea Pig Maximization)
- Cytotoxicity - MEM Elution
- Hemolysis - Direct Contact
- Pyrogenicity - Material Mediated
- Genotoxicity
- Mouse Lymphoma.

Additional *in vivo* testing was performed to establish hemocompatibility and thrombogenicity of the Stent implant alone and of the combined Neuroform™ Microdelivery Stent System.

All test results met the acceptance criteria and demonstrated that the Stent alone and the combined Neuroform™ Microdelivery Stent System were biocompatible, hemocompatible, nontoxic, and nonmutagenic.

Sterility

The Neuroform™ Microdelivery Stent System is sterilized using ethylene oxide (EO). The EO cycle was validated to a sterility assurance level of 10^{-6} per ISO 11135. The System was tested and met specifications after two sterilization exposures.

Shelf Life

A 1-year shelf life was validated using a combined real time and accelerated aging study of finished devices. Package integrity testing included pouch seal integrity, label integrity, dye penetration, pouch burst, and ship testing. Device functionality testing included System functionality testing, Stent characteristic testing (length, diameter, and Austenite finish (A_f)), 3F Microdelivery Catheter characteristic testing, 2F Stabilizer Catheter characteristic testing, and Peelable Sheath characteristic testing (see ***Mechanical Testing*** Section below). Both package integrity and device testing met specifications to support a 1-year expiration date.

Magnetic Resonance Imaging (MRI) Compatibility

The Stent was shown to be MRI compatible in MRI systems operating at a field strength of 1.5 Tesla or less. MRI laboratory evaluation demonstrated that no significant image distortion or heating was created by the presence of the Stents at scanning sequences commonly used during MRI procedures for the given test.

Mechanical Testing

All mechanical testing was performed on the finished, sterile Neuroform™ Microdelivery Stent System, as well as on individual components of the System. All system functionality testing and individual component testing passed the acceptance criteria.

System functionality testing included:

- Verification of Stent Integrity
- Verification of Trackability of System over Guidewire
- Verification of Trackability of System Passage through a Guide Catheter
- Verification of Stent Accessibility of Target Deployment Zone
- Verification of Stent Deployability in Target Deployment
- Verification of Self-Expansion of Stents.

Stent component testing included:

- Stent Potentiodynamic Polarization Test
- Direct Galvanic Coupling Test
- Stent Fatigue Life Testing
- Finite Element Re-Analysis
- Verification of Stent Free Area
- Stent Length Calculation Verification
- Strut Spacing Calculations for Stent "Pore Size" Verification
- Actual Deployed Stent Length Verification
- Actual Deployed Stent Outer Diameter Verification
- Stent Hydrogen Content Test
- Verification of Stent Radial Pressure
- Verification of Stent Contact Pressure
- Verification of Stent Recoil
- Verification of Stent Platinum Markerband Joint
- Stent Surface Characterization.

3F Microdelivery Catheter component testing included:

- Verification of Hub Taper
- Verification of Lumen Diameter
- Verification of Outer Diameter (Markerband)
- Verification of Outer Diameter (Mid-Joint)
- Verification of Catheter Length
- Verification of Catheter Distal Flexible Length
- Verification of Middle Flexible Transition Zone
- Hub Air Aspiration Test
- Markerband Removal Force
- Distal Joint Break Force
- Center Joint Break Force
- Hub Bond Break Force
- Verification of Catheter Integrity
- Verification that Catheter is Free of Particulate.

Peelable Sheath component testing included:

- Outer Diameter Verification Test
- Inner Diameter Verification Test
- Length Test
- Peelability Test.

2F Stabilizer Catheter component testing included:

- Verification of Hub Taper
- Verification of Lumen Diameter
- Verification of Outer Diameter (Markerband)
- Verification of Outer Diameter (Mid-Joint)
- Verification of Stabilizer Length
- Verification of Stabilizer Distal Flexible Length
- Hub Air Aspiration Test
- Markerband Removal Force
- Mid-Joint Break Force
- Hub Bond Break Force
- Verification of Catheter Integrity.

Rotating Hemostasis Valve component testing included:

- Female Luer Hub Test
- Male Luer Hub Test
- Leak Test
- Valve Maximum Outer Diameter Test.

Animal Testing

Earlier versions of the subject Stent were tested in 35 New Zealand rabbits in which wide neck aneurysms were created at the origin of the right common carotid artery. The study had several purposes including assessing the technical feasibility of the delivery system, the ability to tightly pack the aneurysm with coils, and the stability of the coil bundles. The Stent deployed successfully in 33 of 35 cases. Transient adverse events occurred in 3 of 35 cases.

Animals were sacrificed for analysis at 30 days (10 animals), 90 days (15 animals), and 180 days (10 animals). Excised vessel and organ samples were submitted for histopathology, scanning electron microscopy, and morphometric analyses. The findings showed 30-day and 90-day mild to moderate circumferential neointimal hyperplasia and a reduction in the thickness of the neointima at 180 days. The internal elastic lamina remained generally intact with smooth muscle cell maturation and contraction at 180 days. There were minimal to mild inflammatory changes consisting of macrophages and rare giant cells associated with the Stent struts at 30 days with no giant cells seen at 90 days and 180 days. The Stent was completely endothelialized within 30 days. No inflammatory reaction was observed through 180 days.

With respect to angiographic assessment, the study found that 9 of 10 animals exhibited 100% aneurysm occlusion at 30 days, 12 of 15 animals exhibited 100% aneurysm occlusion after 90 days, and 8 of 10 animals exhibited 100% occlusion at 180 days. There was no angiographic evidence of parent vessel stenosis in the immediate post-implant or follow-up films.

Based on this animal study, the Neuroform™ Microdelivery Stent System can be safely deployed and implanted in rabbit carotid arteries. No adverse hematologic, histologic, thrombogenic, or morphologic responses were observed. There was no angiographic evidence of parent vessel stenosis or flow abnormalities during implantation or follow-up. Acute and subacute thrombosis of the Stents and delivery system (acute only) were unremarkable.

X. SUMMARY OF CLINICAL INFORMATION

This was a European clinical study. The patient inclusion criteria were: (1) wide neck, ruptured or unruptured, saccular, intracranial aneurysm or aneurysm on the level of the skull base, where a wide neck is defined as a dome-to-neck ratio <2 and/or neck length of ≥4mm; (2) aneurysm is in artery with diameter ≥1.5mm and ≤5.5mm; (3) patient is ≥18 years old; and (4) patient provided written informed consent.

There were 31 patients entered into the study. Five (16%) were male and 26 (84%) were female. Fifty-two percent of the patients were asymptomatic prior to treatment. Two of the 31 patients did not receive the Stent because of failure to access based on anatomy. The remaining 29 patients enrolled in the study had 30 aneurysms (1 patient had 2 aneurysms that were treated with one Stent). Previous attempts had been made to treat 17 of the 30 aneurysms (57%) using other devices.

Table 4 summarizes the locations of the 30 aneurysms. Table 5 summarizes the sizes of the 30 aneurysms.

Table 4: Aneurysm Location

Location	#	%
Carotid ophthalmic	7	24%
Posterior communicating artery	7	24%
Carotid cavernous	5	17%
Anterior choroidal	2	7%
Basilar tip	2	6%
Carotid bifurcation	1	3%
Middle cerebral artery	1	3%
Anterior cerebral artery	1	3%
Vertebral artery	1	3%
Posterior inferior cerebellar artery	1	3%
Basilar trunk	1	3%
Other	1	3%

Table 5: Aneurysm Size

Measurement	#	Mean	SD	Min	Max
Dome width (mm)	30	7.4	4.3	2.1	20.0
Neck length (mm)	30	4.9	1.8	2.1	11.0
Dome to neck ratio	30	1.5	0.5	0.8	2.7
Parent vessel pre-aneurysm (mm)	30	3.6	0.6	2.4	4.8
Parent vessel post-aneurysm (mm)	30	3.2	0.7	1.7	4.4
Parent vessel caliber differential (mm)	30	1.0	1.0	0.3	1.7

The 29 patients were implanted with 39 Stents to treat their 30 aneurysms. Twenty (69%) patients had 1 Stent, 8 (28%) patients had 2 Stents, and 1 (3%) patient had 3 Stents. The Stents implanted ranged from 3.5mm to 4.5mm. One patient required a secondary endovascular procedure to place a second Stent in the correct location because the original Stent was inadvertently not deployed at the aneurysm site; this counts for 2 of the Stents. One patient had

the original Stent successfully deployed but the Stent was removed during the embolic coiling procedure when the clinical study investigator attempted to snare the errant coil loop and dislodged the Stent. A replacement Stent was implanted in its place, and this counts for 2 of the Stents. For 7 patients, multiple Stents were used to treat one aneurysm in cases where (1) the embolic coiling procedure left the tail of an embolic coil in the vessel or (2) the neck of aneurysm was estimated at an incorrect width and a second or third Stent was necessary to cover the neck of the aneurysm.

With regard to patient accounting, 31 patients were originally entered into the study; however, 2 did not receive the Stent. One patient died immediately after the procedure. There are adverse event data on 29 patients, including the one death. Therefore, there were 28 patients of 31 who were expected for evaluation through 6 months. At discharge, 28 of the expected 28 were evaluated for a follow-up rate of 100%. At 6 months, 26 of 28 patients were evaluated for a follow-up rate of 93%.

The study endpoints were (1) adverse events, (2) technical feasibility, and (3) clinical outcome. The incidence of all adverse events, device or procedure-related, were assessed. Technical feasibility was assessed by the ability to access the aneurysm and place the Stent accurately across the aneurysm neck. Clinical outcome was assessed by percent angiographic aneurysm occlusion

Adverse events were presented in Tables 2 and 3 in Section VIII above.

Table 6 below summarizes the patient rates with regard to technical feasibility.

Table 6: Technical Feasibility

Technical Feasibility	n/(%)
Ability to access aneurysm	29/31 (93.5%) patients[1]
Ability to place Stent across neck	29/29 (100%) patients[2,3]

[1]Two patients could not be accessed based on anatomy.
[2]One patient required a secondary endovascular procedure to place a second Stent in the correct location because the original Stent was inadvertently not deployed at aneurysm site.
[3]There were 2 intraoperative device malfunctions involving the markerband of the 2F Stabilizer Catheter inadvertently detaching from the shaft of the 2F Stabilizer Catheter after Stent deployment. In one patient, the 2F Stabilizer Catheter was inside the patient at the time of the device malfunction, and the separated markerband embolized in a small, distal intracranial artery. This patient had no adverse events from this event. In the second patient, the 2F Stabilizer Catheter was outside the patient at the time of the device malfunction. SMART Therapeutics has since increased its markerband bond strength.

Table 7 below summarizes the patient rates with regard to clinical outcome.

Table 7: Clinical Outcome

Clinical Outcome	n (%)
% occlusion at discharge[2]	
100%	17 (58.6%)
95-99%	13 (44.8%)
% occlusion at 6 months	
100%	18 (69.2%)
95-99%	8 (30.8%)

[1]The "n" reflects the number of occurrences. The % is based on 29 patients at discharge and 26 patients at 6 months.
[2]One patient had 2 aneurysms, each with different resulting % occlusion. Therefore, this patient is reported twice.

Other clinical outcomes included:

- No Stent stenosis or migration.
- No embolic coil migration.
- No parent vessel thrombosis, occlusion, or dissection.
- Neurological status: Of 26 patients evaluated at 6 months, 17 (65%) had an unchanged (normal) neurological assessment as compared to baseline, 3 (16%) had an improved (from abnormal to normal) neurological assessment as compared to baseline, 5 (19%) had an unchanged (abnormal) neurological assessment as compared to baseline, and 1 (4%) had a worsened (abnormal moderate confusion to abnormal severe confusion) neurological assessment as compared to baseline.

XI. RISK/PROBABLE BENEFIT ANALYSIS

As stated in Section VI above, there are limitations to the alternative treatments for wide neck aneurysms. The Neuroform™ Stent is designed to address the limitations associated with coiling of wide neck aneurysms that are not amendable to treatment by clipping by combining two endovascular techniques (stents and coils). First, the Neuroform™ Stent is placed across the neck of the aneurysm. Second, the embolic coil delivery catheter is passed between the struts of the Stent to obtain and maintain dense coil packing within the aneurysm. The Neuroform™ Stent stabilizes the neck of the aneurysm and acts as a physical barrier to stabilize embolic coils and minimize coil protrusion and/or embolization.

Clinical study data on the Neuroform™ Microdelivery Stent System were provided. Adverse events, technical feasibility, angiographic and clinical outcome were reported for 29 patients at discharge and 26 patients at 6 months. Patients with ruptured and unruptured aneurysms were treated.

There were 12 serious adverse events in 5 patients. There were 21 other adverse events. All adverse events occurred prior to or by the time of discharge; none occurred between discharge and the 6-month timepoint. The one patient death was not related to the device. Table 2 of Section VIII summarizes the patient rates for observed serious adverse events. Table 3 of Section VIII summarizes the patient rates for all other observed adverse events.

Variable adverse event rates for endovascular treatment of wide neck aneurysms are reported in the medical literature. This variability is related to differences in patient selection criteria, patient outcome measures, follow-up duration, and small sample sizes for coiling studies. However, within the context of the adverse event rates reported in the medical literature, there is no evidence that patients will be exposed to an unreasonable or significant risk of injury from use of the Neuroform™ Microdelivery Stent System as compared to coiling as a means of treatment for wide neck aneurysms.

In terms of the clinical benefit of the Neuroform™ Microdelivery Stent System, 100% (26 of 26 patients) had ≥95% occlusion of their aneurysm(s) and 96% (25 of 26 patients) had no deterioration in neurological status at 6-month follow-up. Aneurysm occlusion of ≥90% is generally considered successful by the clinical community.

Extensive mechanical testing was performed on the Neuroform™ Microdelivery Stent System, as a whole, as well as on the individual components. All tests met the stated acceptance criteria. Animal testing provided evidence that the Neuroform™ Microdelivery Stent System could be safely deployed and implanted in rabbit carotid arteries. Refer to Section IX for details.

Therefore, it is reasonable to conclude that the probable benefit to health from using the Neuroform™ Microdelivery Stent System with embolic coils for wide neck aneurysms outweighs the risk of illness or injury when used in accordance with the instructions for use and when taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

XII. PANEL RECOMMENDATION

Review of this HDE application was performed by a member of the Neurological Devices Advisory Panel. The Panel member stated that the Neuroform™ Stent offers a probable benefit in the endovascular management of wide neck aneurysms and that there is no evidence that patients will be exposed to an unreasonable or excessive risk of injury from use of the device. It was determined that the preclinical and clinical issues raised by the HDE did not require full Panel review.

XIII. CDRH DECISION

CDRH determined that, based on the data submitted in the HDE, the Neuroform™ Microdelivery System will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the System with embolic coils for the treatment of wide neck, intracranial, saccular aneurysms that are not amenable to treatment with surgical clipping outweighs the risks of illness or injury, and issued an approval order on September 11, 2002.

XIV. APPROVAL SPECIFICATIONS

Indications for Use: See *Instructions for Use* (Attachment 1)

Information for the Patient: See *Patient Brochure* (Attachment 2)

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the *Instructions for Use* (Attachment 1).

XV. REFERENCES

None