Summary of Safety and Probable Benefit

Elana Surgical Kit_{HUD}

H080005

I. General Information

Device Generic Name: Arteriotomy System

Device Trade Name: Elana Surgical Kit_{HUD}

Applicant's Name and Address: Elana bv
Yalelaan 44
3584 CM, Utrecht
The Netherlands

Humanitarian Device Exemption (HDE) Number: H080005

Humanitarian Use Device (HUD) Designation Number: 03-0108

Date of Humanitarian Use Device (HUD) Designation: September 26, 2003

Date(s) of Panel Recommendation: None

Date of Good Manufacturing Practice Inspection: March 23-26, 2009

Date of Notice of Approval to Applicant:

II. Indications for Use

The Elana Surgical KitHUD, when connected to the Spectranetics Xenon-Chloride Laser Model CVX-300, is indicated for creating arteriotomies during an intracranial vascular bypass procedure in patients 13 years of age or older with an aneurysm or a skull base tumor affecting a large [> 2.5 mm], intracranial artery that failed balloon test occlusion, cannot be sacrificed, or cannot be treated with conventional means due to local anatomy or complexity.

III. Contraindications

The Elana Surgical Kit_{HUD} should not be used:

- on graft vessels that show signs of arteriosclerosis or calcification; or
- when flow in the recipient artery is interrupted or reduced; or
- on a recipient artery whose lumen is constricted at the anastomosis site or during attachment of an Elana Ring; or
- on a site where the catheter with donor graft is not perpendicularly accessible to the recipient vessel; or

- on a recipient artery that has a wall thickness greater than that of a human internal carotid artery or identified to have an abnormality like an unusually high or low wall thickness, calcification, or detachable layers in the wall (which could cause the laser light to cut less effectively through the wall); or

- on a recipient artery with a foreign material like stents or suture at or beneath the anastomosis site; or

- on an aneurysm itself; or

- when contact of the catheter tip with the recipient artery wall is hindered or made difficult by a thick donor graft wall or a small donor graft lumen.

IV. Warnings and Precautions

Warning:

If the circular disk of tissue is not retrieved with the Elana Catheter, it is likely still attached to the artery wall and is considered a retained flap. When a retained flap exists, the surgeon should assess the flap and consideration should be given to its removal since there is a potential for a retained flap to embolize when not removed manually.

The rate of flap retention in one clinical study was 22% (8/37 device uses in 33 subjects). In 5 of those 8 cases, the flap was manually retrieved with 1 severe adverse event (a diffuse subarachnoid hemorrhage and thrombosis of a basilar aneurysm with compression of the ventral pons) observed. In the 3 cases where no flap was retrieved, there was 1 severe adverse event consisting of an aneurysm rupture during manipulation/inspection of distal anastomosis and subsequent stroke.

One patient with a retained flap experienced an embolic stroke immediately post-procedure in a series of 330 European cases, and embolization of the retained flap could not be ruled out in this case.

See additional *Warnings and Precautions* in device labeling.

V. Device Description

The Elana Surgical Kit_{HUD} consists of the Elana Arteriotomy $System_{HUD}$ and extension tubing for connection to a vacuum source. The Elana Arteriotomy $System_{HUD}$ is comprised of the Elana Catheter and the Elana Rings.

The Elana Surgical Kit_{HUD} should only be used with the US legally marketed Spectranetics XeCl (Xenon-Chloride) Excimer Laser System, Model CVX-300. This laser system will allow the surgeon to:

- measure the catheter output pulse energy and set it to the desired value without impairing the function of any of the fibers of the Elana Catheter; and
- deliver at the distal tip of the Elana Catheter, a 5 second pulse train of 200 pulses at 40 Hz and wavelength of 308 nm. Each pulse is of a duration of 125-200 ns and a pulse energy of 10mJ (average 400 mW).

All Elana Surgical Kit components are sterile and for single patient use during one surgical procedure only. Each part of the kit is not to be re-used.

Elana Ring

The Elana Ring is a flat ring implant constructed of platinum. It is available in two configurations: the first (model 2.6) has an inner diameter of 2.6 mm and an outer diameter of 3.1 mm, the second (model 2.8) has an inner diameter of 2.8 mm and outer diameter of 3.3 mm. The wall thickness of both Rings is 0.25 mm. The Elana Ring is designed to define the exact location of the arteriotomy site on the recipient vessel and is connected along with a donor graft to the recipient artery wall using conventional micro-neurosurgery suturing techniques. The Ring helps to ensure a flush interface between the laser tip and the arteriotomy site, and thereby allows the laser tip to broach the arterial wall along the Ring's circumference.

Elana Rings 2.6 and 2.8 are marked with different colored sutures (White for Elana Ring 2.6 and Green for Elana Ring 2.8) to help the surgeon identify the size of the ring.

The Elana Ring has MR (magnetic resonant) Conditional labeling.

Elana Catheter 2.0

The Elana Catheter 2.0 is a catheter that provides vacuum through the central lumen, and delivers laser light to cut an arteriotomy. The catheter is 130 inches long with an outer diameter of 2.0 mm at the distal tip. The catheter has a stainless steel distal tip with silica glass laser fibers configured in a ring around the distal tip.

The Elana Catheter 2.0 should only be attached to the Spectranetics XeCl (Xenon-Chloride) Excimer Laser System, Model CVX-300.

Operating Steps

The Elana Surgical Kit_{HUD} replaces the scalpel or micro scissors used in a conventional arteriotomy. It does not create an anastomosis or bypass.

An overview of the operating steps for the ELANA Surgical Kit_{HUD} are provided below. (Device users should refer to the full Operating Instructions for the warnings, precautions, and reminders):

- After preparation and selection of an anastomosis site on one of the major cerebral arteries, the surgeon places the Elana Ring onto the artery wall (See Figures A, B, C below) to confirm the suitability of the site.

- The surgeon attaches the Elana Ring together with the donor graft to the artery wall (See Figure D below) using a fine suture.

- The connection of the graft to the artery is checked for leakage using saline solution and tightened further with additional suture if required.

- The surgeon then points the distal tip of the fiber optic catheter directly at the center of the energy detector and one to two inches away from the energy detector to calibrate the laser and ensure that 10mJ of laser light per pulse at 40 Hz is emitted The red visible beam is provided to assist in centering. The catheter is connected to an aspiration system via an extension line connected to the proximal end of its bifurcation. After activating aspiration, the surgeon covers the catheter tip and gently lifts it to confirm vacuum.

- Once the above checks are completed, the surgeon inserts the distal end of the Elana Catheter into the donor graft until the tip evenly touches the artery wall inside the Elana Ring (See Figure E below).

- Apply suction by activating the vacuum source according to its instructions for use with maximum vacuum. The suction exerted by the vacuum on the recipient artery wall can be felt by briefly pulling slightly; ensure not to lift or move the artery unduly. For about 2 minutes the catheter tip should be held in steady contact with the artery wall, neither pushing, nor pulling nor tilting nor twisting nor moving.

- After the two minutes, the surgeon then activates the Excimer laser (by pressing the footswitch). As a result, a train of 200 pulses is delivered (5 seconds at 40Hz) accordingly. When 200 pulses are delivered, the laser will stop automatically and the footswitch of the laser must be released

- After the laser has stopped, the surgeon slowly removes the Elana Catheter (see Figure F below) while not exerting force onto the artery or the graft.

- The surgeon then checks for a retrograde blood flow through the donor graft before occluding it. The ELANA technique is completed for the first arteriotomy required for the bypass.

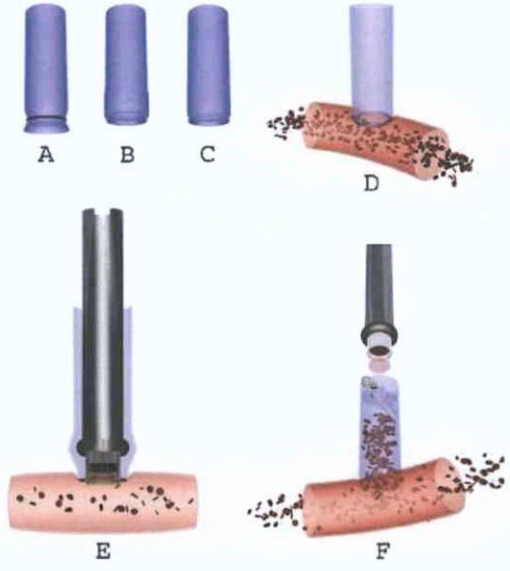

Figure: Operating Steps

VI. Alternative Practices and Procedures

There are limited treatment options for an adult patient with an aneurysm or a skull base tumor affecting a large, intracranial artery that failed balloon test occlusion, cannot be sacrificed, or cannot be treated with conventional means due to local anatomy or complexity. Traditionally, aneurysms and/or tumors that cannot be treated via endovascular means are treated surgically by cutting off blood flow through the affected area while a bypass graft is placed.

VII. Marketing History of the Device

The Elana Arteriotomy System was CE (Conformité Européenne) certified on October 10, 2005. The Elana Arteriotomy System has been available for sale in the European Union and European Free Trade Association countries (Norway, Iceland, Switzerland and Liechtenstein) since January 2006.

The Elana Surgical Kit was licensed for sale in Canada on November 15, 2007.

VIII. Adverse Effects of the Device on Health

A. Investigational Device Exemptions (IDE) Study Data

This section describes the adverse effects observed with the use of the Elana Surgical Kit in 33 subjects enrolled in a prospective, multi-center study conducted under an approved Investigational Device Exemptions (IDE) application. The 33 subjects have all completed their 30 days post-bypass follow-up per protocol.

An independent Clinical Events Committee (CEC) has adjudicated all the serious adverse events The severity of an adverse event was assessed by the CEC on the basis of its clinical judgment and the following definitions. The condition of the subject before the surgery and the required treatment was also considered in this assessment.

a. None: no adverse event. Device- and procedure relatedness are not applicable.
b. Mild: an adverse event that is noticeable to the subject. The mRS (modified Rankin Scale) may temporarily be increased but returns to the state prior to the surgery.
c. Moderate: an adverse event that interferes with the subject's activities in the long term. The mRS may permanently be increased when compared to before the operation, but is still well acceptable in proportion to the condition before the operation and the threat posed by this condition.
d. Severe: an adverse event that causes death or is severely and permanently disabling that is more severe than a moderate event.

A Serious Adverse Event is defined as an event that:

a. Led to death
b. Led to a serious deterioration in the health of the patient that:

   - Resulted in life-threatening illness or injury
   - Resulted in permanent impairment of a body structure or a body function
   - Required in-patient hospitalization or prolongation of existing hospitalization
   - Resulted in medical or surgical intervention to arrest permanent impairment to body structure or a body function
   - Led to fetal distress, fetal death or a congenital abnormality or birth defect

An unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

In the IDE study, a total of 37 devices were used on 33 subjects. In 4 subjects, the Elana Surgical Kit_{HUD} was used for both the proximal anastomosis and the distal anastomosis. See Tables 1 and 2 below for a summary of adverse events. Table 1 depicts the reported Serious Adverse Events, while Table 2 shows all the Non-serious Adverse Events.

There were a total of three (3/33; 9%) device related (severe or moderate adverse) events which included diffuse subarachnoid hemorrhage and thrombosis of basilar aneurysm with compression of the ventral pons (1), bypass occlusion (1), and aneurysm rupture during manipulation/inspection of distal anastomosis and subsequent stroke (1).

There were three (3/33; 9%) deaths and five (5/33; 15%) non-fatal strokes. Of the three subjects that died, one case was determined to be definitely not device related, one case was likely device related and definitely procedure related, and the third

case was one moderate adverse event likely device related. With respect to the five non-fatal strokes, there was one determined to be likely device related.

No unanticipated adverse device effects have occurred during the IDE study.

Tables 1 and 2 summarize the serious adverse events (SAEs) and other adverse events (AEs).

Table 1: Serious Adverse Events in the IDE Study

Reason for surgery	Serious Adverse Event	N	Severity/ Subject ID	Time of Onset	Outcome
ID1:aneurysm ID2:aneurysm ID3:Tumor	ID 1: Brainstem infarction / diffuse subarachnoid hemorrhage / thrombus of basilar aneurysm with compression of the ventral pons ID 2: Intra-operative subarachnoid hemorrhage/large pseudoaneurysm of basilar artery / massive brain edema ID 3: Stroke	3	Severe/ ID 1 ID 2 ID 3	Post-operative (3)	Death (3)
Aneurysm in all cases	Non fatal Stroke	5	Severe: ID 5,6,8 Mild: ID 4,7	Intra-operative (ID5,8) Post-operative (ID4,6,7)	mRS at 30 days post op higher than pre-operatively (5) namely: ID1:1; ID2:4; ID3:4; ID4:1; ID5:4
Aneurysm	Right saphenous vein graft, wound dehiscence plus infection leading to bacteremia plus fever	1	Severe / ID 9	Post-operative	Symptoms resolved by 30 days
Aneurysm	Intracerebral hemorrhage under heparinization and hypertension in ICU	1	Moderate/ ID 4	Intra-operative	Symptoms resolved by 30 days
Aneurysm	Dissection of left common carotid artery during diagnostic angiogram	1	Mild/ ID 10	Post-operative	Symptoms resolved by 30 days
Aneurysm	Left leg deep vein thrombosis (DVT): Left femoral and lower extremity DVT	1	Mild / ID 9	Post-operative	Symptoms resolved by 30 days
Aneurysm	Aneurysm bleeding	1	Mild/ ID 11	Intra-operative	Symptoms resolved by 30 days.
Aneurysm	Increased brain swelling in the frontal lobe	1	Severe / ID 5	Post-operative	Symptoms resolved by 30 days.
Aneurysm	Intracerebral hemorrhage and cerebral edema	1	Severe / ID 5	Post-operative	Symptoms resolved by 30 days.
Aneurysm	Unable to complete bypass (due to aneurysm rupture)	1	Severe / ID 5	Intra-operative	Symptoms resolved by 30 days.
Aneurysm	Right hip fracture	1	None /ID 6	Post-operative	Symptoms resolved by 30 days.

Table 2: Other Adverse Events in the IDE Study

Reason for surgery	Adverse Event	N	Severity/ Subject ID	Time of Onset
Ischemia: ID 12 Tumor: ID 3 Aneurysm: ID 2, 14	Bypass occluded	4	Severe: ID 14 Moderate: ID 2,3 None: ID 12,13	Post-operative (4)
Aneurysm in all cases	Aphasia(Motor)	2	Moderate / ID 10, 15	Post-operative(2)
Aneurysm in all cases	Hydrocephalus	2	None: ID 8 Moderate: ID 13	Post-operative (2)
Aneurysm in all cases	Hemiparesis	3	Moderate: ID16 Mild: ID17,18	Post-operative (3)
Aneurysm in all cases	Urinary tract Infection	3	Mild / ID 8, 9, 13	Post-operative (3)
Aneurysm in all cases	Change in neurological status/exam	3	Mild / ID 2, 14, 16	Post-operative (ID 2, 14, 16)
Aneurysm in all cases	Worsening speech difficulties	2	Mild/ ID 17, 19	Post-operative (2)
Aneurysm in all cases	Expressive aphasia	2	Mild / 2 x ID 20	Post-operative (2)
Aneurysm in all cases	Pulmonary edema	2	Mild / ID 10, 16	Post-operative (2)
Aneurysm in all cases	Reduced hemoglobin/hematocrit	2	Mild / ID 1, 17	Post-operative (2)
Aneurysm in all cases	Anemia	2	Mild / ID 5, 13	Post-operative (2)
Aneurysm	Grand-mal seizure	1	Severe/ ID 15	Post-operative
Aneurysm	Cellulitis	1	Moderate / ID 7	Post-operative
Aneurysm	Exacerbation of congestive heart failure	1	Moderate / ID 16	Post-operative
Aneurysm	Elevated liver function tests	1	Moderate / ID 19	Post-operative
Aneurysm	Bibasilar airspace opacifications in lung	1	Moderate / ID 1	Post-operative
Aneurysm	Intermittent hypotension	1	Moderate / ID 5	Post-operative
Aneurysm	Respiratory failure	1	Moderate / ID 5	Post-operative
Aneurysm	Central diabetes insipidus	1	Mild / ID 5	Post-operative
Aneurysm	Pneumonia	1	Mild / ID 9	Post-operative
Aneurysm	Moto plegia	1	Mild /	Post-operative

			ID 15	
Aneurysm	Subdural hematoma	1	Mild / ID 17	Post-operative
Aneurysm	Periorbital edema	1	Mild / ID 19	Post-operative
Aneurysm	Periorbital ecchymosis	1	Mild / ID 19	Post-operative
Aneurysm	Facial edema	1	Mild / ID 19	Post-operative
Aneurysm	Headache	1	Mild / ID 19	Post-operative
Aneurysm	Mild right sided weakness	1	Mild / ID 20	Post-operative
Aneurysm	200 cc blood loss during procedure	1	Mild/ ID 10	Intra operative
Aneurysm	Myocardial injury	1	Mild / ID 10	Post-operative
Aneurysm	Hyponatremia	1	Mild / ID 10	Post-operative
Aneurysm	Hypersensitivity to right leg surgical incision	1	Mild / ID 14	Post-operative
Aneurysm	Hypertension	1	Mild / ID 13	Post-operative
Aneurysm	Rash, leucopenia, eosinophilia secondary to Dilantin treatment	1	Mild / ID 9	Post-operative
Aneurysm	Perforator infarct	1	Mild / ID 21	Post-operative
Aneurysm	Leukocytosis	1	Mild / ID 16	Post-operative
Aneurysm	Small ischemic, non symptomatic stroke	1	Mild / ID 16	Post-operative
Aneurysm	Seizure - pre-ELANA	1	None / ID 22	Intra-operative
Aneurysm	Diffuse cerebral edema on CT scan	1	None / ID 14	Post-operative
Aneurysm	Ischemic changes within the right frontal lobe on CT scan	1	None / ID 14	Post-operative
Aneurysm	MRAof head demonstrates infarct in right frontotemporal regions	1	None / ID 14	Post-operative
Aneurysm	Extensive bilateral DVT extending from calf to external iliac veins	1	None / ID 22	Post-operative

B. Retrospective European Data

This section describes the adverse effects observed with the use of the Elana Arteriotomy System in retrospectively collected data on a total of 330 subjects treated with the Elana Arteriotomy System in Europe [Utrecht (The Netherlands), Mannheim (Germany), Helsinki (Finland), Bern (Switzerland), London (United Kingdom), Naples (Italy) and Göteborg (Sweden)] during the period from 1993 to 2006. From 1993 to 2005, an experimental version of the Elana Arteriotomy System was used, while as of 2006 the commercial CE Marked system was used. The commercial CE Marked system is identical to the U.S. IDE device.

An independent reviewer/adjudicator classified the adverse events reported by Dr.Tulleken in Utrecht in which post-operative mRS score was worse than the pre-operative score to determine whether there had been a retained/unknown flap status and a complication occurred within two weeks post-operatively. This independent reviewer also adjudicated all surgeries performed in Helsinki and Mannheim. There were a total of 375 devices used on 330 subjects. There were 24/330 (7%) deaths and 17 (5%) non-fatal strokes. No unanticipated adverse device effects occurred in the European cohort.

Table 3 describes all cases/events in the European Cohort in the period 1993-2006 where the severity was severe, moderate or mild.

Table 3 Adverse Events in Retrospective European Study

Reason bypass	Adverse Event	N	Time of onset	Severity
Aneurysm: ID4, ID6, ID38, ID41, ID42,ID46, ID49, ID52, ID60, ID65, ID68, ID69, ID71, ID76, ID82, ID84 Ischemia: ID8, ID9, ID40, ID44, ID48, ID59, ID67, ID74 Tumor: ID45, ID47	Hemiparesis	26	Post-op	Severe: ID4, ID6, ID8, ID9, ID38 Moderate: ID40, ID41, ID42, ID44, ID45, ID46, ID47, ID48, ID49, ID52 Mild: ID59, ID60, ID65, ID67, ID68, ID69, ID71, ID74, ID76, ID82, ID84
Aneurysm: ID6, ID11, ID12, ID23, ID24, ID28, ID37, ID38, ID41, ID46, ID53, ID71, ID72, ID75, ID83, ID84 Ischemia: ID8, ID44, ID46, ID74	Bypass occlusion	20	Intra-op: ID55 Post-op: ID6,ID8, ID11, ID12, ID23, ID24, ID28, ID37, ID38, ID41, ID44, ID46, ID53, ID71, ID72, ID74 ID75, ID83, ID84	Severe: ID6, ID8, ID11, ID12, ID23, ID24, ID28 , ID37, ID38 Moderate: ID41, ID44, ID46 Mild: ID53, ID55, ID71, ID72, ID74, ID75, ID83, ID84
Aneurysm: ID6, ID10, ID21, ID22, ID24, ID28, ID37, ID46, ID63, ID85 Ischemia: ID5, ID9 Tumor: ID45	(Brain) Edema	13	Post-op	Severe: ID5, ID6, ID9, ID10, ID21, ID22, I ID24, ID28, ID37 Moderate: ID45, ID46 Mild: ID63, ID85
Tumor: ID2 Aneurysm: ID3, ID12, ID13, ID16, ID23, ID65 Ischemia: ID27	High intracranial pressure	8	Post op	Severe: ID2, ID3, ID12, ID13, ID16, ID23, ID27 Mild: ID65
Ischemia: ID5, ID7, ID8, ID48 Aneurysm: ID4, ID11, ID36, ID51	Brain infarction / stroke	8	Post-op	Severe: ID4, ID5, ID7, ID8, ID11, ID36 Moderate: ID48, ID51
Aneurysm: ID13, ID17, ID24, ID28, ID81 Ischemia: ID19	Subdural/epidural hematoma	6	Post-op	Severe: ID13, ID17, ID19, ID24, ID28 Mild: ID81
Aneurysm: ID22, ID24, ID54 Ischemia: ID15, ID67	Hydrocephalus	5	Intra-op: ID24 Post-op: ID15, ID22, ID54, ID67	Severe: ID15, ID22, ID24 Mild: ID54, ID67

Reason bypass	Adverse Event	N	Time of onset	Severity
Aneurysm: ID18, ID25, ID35, ID50, ID72	SAH	5	Post-op	Severe: ID18, ID25, ID35 Moderate: ID50 Mild: ID72
Aneurysm	Aneurysm bleeding	4	Intra-op: ID23 Post-op: ID3, ID23, ID39	Severe: ID3, ID23 (2x) Moderate: ID39
Aneursym: ID 24, ID32 Ischemia: ID19, ID26	Intracranial hemorrhage.	4	Intra-op: ID24 Post-op: ID19, ID26, ID32	Severe: ID19, ID24, ID26, ID32
Aneurysm: ID 20, ID29 Tumor: ID47	Intracerebral hematoma	3	Post-op	Severe: ID20, ID29 Moderate: ID47
Aneurysm: ID20, ID25	Brain stem compression	2	Post-op	Severe: ID20, ID25
Aneurysm: ID30, ID33	Thrombosis of basilar artery following endovascular intervention	2	Post-op	Severe: ID30, ID33
Aneurysm	Intraventricular and intraparenchymal hemorrhage.	1	Post-op	Severe: ID3
Ischemia: ID1	Bypass torn off from arteriosclerotic vessel wall.	1	Intra-op	Severe: ID1
Ischemia: ID1	Gastric perforation.	1	Post-op	Severe: ID1
Ischemia	Bypass abandoned	1	Intra-op	Severe: ID5
Ischemia	Pneumonia	1	Post-op	Severe: ID8
Ischemia	Progressive anterolateral cardiac ischemia	1	Post-op	Severe: ID9
Aneurysm	Incontrollable blood pressure changes	1	Intra-op	Severe: ID10
Aneurysm	Clot in bypass	1	Intra-op	Severe: ID11
Aneurysm	Compression of brain stem after coiling aneurysm.	1	Post-op	Severe: ID14
Aneurysm	Basilar syndrome caused by thrombosing aneurysm	1	Post-op	Severe: ID14
Aneurysm	Thrombi in M1 and M2 segment causing ischemia	1	Post-op	Severe: ID16

Reason bypass	Adverse Event	N	Time of onset	Severity
Aneurysm	Hemi paralysis	1	Post-op	Severe: ID17
Ischemia	Severe coagulation problems	1	Post-op	Severe: ID19
Aneurysm	Air embolus in the superior sagital sinus	1	Post-op	Severe: ID21
Aneurysm	Thrombosis of stent	1	Post-op	Severe: ID24
Aneurysm	Diffuse hemorrhage	1	Post-op	Severe: ID24
Ischemia	Brain stem ischemia	1	Post-op	Severe: ID27
Aneurysm	Aneurysm rupture	1	Intra-op	Severe: ID31
Aneurysm	Patent bypass caught in drill and torn off	1	Intra-op	Severe: ID34
Ischemia: ID43, ID 44, ID48, ID56, ID59, ID74 Tumor: ID45 Aneurysm: ID50, ID84, ID85	Dysphasia	10	Post-op	Moderate: ID43, ID44, ID45, ID48, ID50 Mild: ID56, ID59, ID74, ID84, ID85
Aneurysm: ID46, ID49, ID62, ID70, ID78, ID79	Aphasia	6	Post-op	Moderate:ID46, ID49 Mild: ID62, ID70, ID78, ID79
Ischemia: ID40, ID55, ID57, ID77	Bone flap infection	4	Post-op	Moderate: ID40 Mild:ID55, ID57, ID77
Aneurysm: ID39, ID62	Hemiplegia	2	Post-op	Moderate: ID39 Mild: ID62
Aneurysm	Partial occlusion stem MCA	1	Post-op	Moderate: ID39
Ischemia	Epileptic insults	1	Post-op	Moderate: ID40
Ischemia	Occulomotor paresis	1	Post-op	Moderate: ID44
Tumor	Epilectic assaults	1	Post-op	Moderate: ID45
Tumor	Recidivating drain infection/ dysfunction	1	Post-op	Moderate: ID47
Ischemia	Visual decrease	1	Post-op	Moderate: ID48
Aneurysm	Occulomotor Palsy	1	Post-op	Moderate: ID49

Reason bypass	Adverse Event	N	Time of onset	Severity
Aneurysm	Spastic paresis	1	Post-op	Moderate: ID50
Aneurysm	Walking difficulties	1	Post-op	Moderate: ID50
Aneurysm: ID78, ID79	Hemorrhage due to retraction	2	Post-op	Mild: ID78, ID79
Aneurysm	Possible occlusion MCA for a few minutes	1	Intra-op	Mild: ID54
Ischemia	TIA's	1	Post-op	Mild: ID55
Ischemia	Cognitive impairment	1	Post-op	Mild: ID56
Aneurysm	Abdominal aorta aneurysm bleeding	1	Post-op	Mild: ID58
Aneurysm	Intermittant vision disturbance	1	Post-op	Mild: ID60
Ischemia	Asymmetric movements	1	Post-op	Mild: ID61
Aneurysm	Hemianopsia	1	Post-op	Mild: ID62
Aneurysm	Sudden severe headache	1	Post-op	Mild: ID64
Aneurysm	Hypocortisolism	1	Post-op	Mild: ID66
Aneurysm	Epidural hemorrhage	1	Post-op	Mild: ID69
Aneurysm	Respiratory insufficiency	1	Post-op	Mild: ID69
Aneurysm	Ophthalmoplegia	1	Post-op	Mild: ID69
Aneurysm	Subdural Hygroma	1	Post-op	Mild: ID73
Aneurysm	Compression of third ventricle	1	Intra-op	Mild: ID75
Aneurysm	Diplopia	1	Post-op	Mild: ID76
Aneurysm	Meningitis	1	Post-op	Mild: ID82
Aneurysm	Vascular damage with laser	1	Intra-op	None/Mild*: ID86

*The reviewer classified the severity of this event as 'none' and 'no adverse event'. However, since this event was device related, Elana bv classified it as mild.

C. "Flap" Retention Data

Following use of the Elana Arteriotomy System, there is a potential for the laser perforation not to be complete and result in a circular disk of tissue (or "flap") being retained on the artery wall. This condition may occur if the Catheter does not completely contact the artery wall within the Ring or if the suture exerts uneven or excessive tension on the artery wall within the Ring. There is a potential for the retained flap to embolize when it is not removed manually. In order to remove the flap, the artery must be occluded. In the five IDE cases for which a flap was manually retrieved, the average arterial occlusion time was 8 minutes (range 5 to 11 minutes).

The rate of flap retention in the IDE clinical study was 22% (8/37 device uses in 33 subjects). In five (5) of those eight (8) subjects with a retained flap, the flap was manually retrieved and in three (3) cases there was no flap retrieved. In 5 of those 8 cases, the flap was manually retrieved with 1 severe adverse event (a diffuse subarachnoid hemorrhage and thrombosis of basilar aneurysm with compression of the ventral pons) observed. In the 3 cases where no flap was retrieved, there was one (1) severe adverse event consisting of an aneurysm rupture during manipulation/inspection of distal anastomosis with subsequent stroke. In one (1) case the flap dissolved, the anastomosis was used and the arteriotomy was successful (patent bypass at seven (7) days post-op), in the other case the Investigators decided to abandon the anastomosis and bypass.

The rate of flap retention in the retrospectively evaluated European (EU) cohort was 26% (96/375 device uses). Data on flap retention were lacking in 4% of the total devices used. Manual flap retrieval was not performed in Utrecht from 1993 to 2003, as their protocol defined that when no flap was retrieved on the catheter (i.e., flap still attached to the artery wall), the bypass was abandoned unless it showed a bypass flow of at least 50 ml/min. Surgeons began to manually retrieve flaps in 2004; therefore, manual flap retrieval has been performed in only 2% (9/375) of device uses in the retrospective EU experience. In 1 of 330 of the European cases, embolization of a retained flap could not be excluded but the subject improved markedly and was active walking (with aid), and talking but was still experiencing severe weakness of the right hand and arm.

IX. Potential Adverse Effects of the Device on Health

The potential adverse effects with the Elana Surgical Kit_{HUD} include:

- The risks from manipulation and perforation of blood vessels. These potential risks include embolic stroke due to incomplete perforation of a vessel, air embolism, infection, distal embolization, thrombosis, vessel dissection or perforation, acute or delayed occlusion, bleeding, ischemia, intracranial hemorrhage, vessel rupture, vessel spasm, recipient vessel and/or graft kinking, anastomic leakage, hydrocephalus, and stroke. These potential risks can result in death or morbidity. Neurologic events may include deficits of various nerves, hemiparesis, hemiplegia, ataxia, loss of hearing or vision, and/or aphasia.

- The risks associated with delivering laser energy to a vessel are similar to the risks listed above for manipulation or perforation of vessels. These include vessel spasm, vessel dissection or perforation, thrombosis, distal embolization, pseudoaneurysm, hemorrhage, infection, and stroke.

- The risks associated with placing a platinum implant ring in a patient include those associated with MRI (magnetic resonant imaging) compatibility, biocompatibility, and embolization.

X. Summary of Pre-Clinical Studies

A. Verification Testing

Devices used for verification testing were assembled and packaged in a controlled environment and sterilized using a double sterilization cycle. All samples passed the tests described in Table 4 in conformity with the respective acceptance criteria. The data demonstrate that the Elana Catheter and Elana Ring sufficiently meet the design specifications and are suitable for their intended use.

Table 4: Verification Testing of the Elana Arteriotomy System

Test	Purpose	Samples Tested†	Acceptance Criteria
Elana Catheter			
Inner Band to Inner Lumen	The bonds must have appropriate strength so they will not separate during use of the device.	10	5 N per ISO 10555-1
Bifurcate Bond		10	15 N per ISO 10555-1
Outer Jacket to Outer Band Bond		10	15 N per ISO 10555-1
Tail to Proximal Coupler		10	15 N per ISO 10555-1
Inner Band to Outer Band Bond		10	15 N per ISO 10555-1
Torque Test of Bifurcate		10	15 N per ISO 10555-1
Grid-to-Inner Band Weld Testing		10	10 N per ISO 10555-1
Polyimide Adhesion Testing	To verify the Polyimide Inner Band achieves acceptable adhesion to the epoxy	11	10 N per ISO 10555-1
Coupling Reliability	To ensure the coupling works properly with the laser.	10	All catheters must pass calibration on three separate lasers.
Proximal & Distal Tip Integrity	To ensure proximal and distal fiber placement is unaffected by laser testing.	10	There should be no significant change in the proximal or distal laser fibers after testing.
Radius Bend Test	To ensure the catheter can be placed around a bend and not experience loss of function.	10	All Catheters must remain functional and demonstrate the ability to calibrate post Radius/Bend Test.
Elana Ring			
Dimensional Inspection	Dimensional measurements should meet specifications	2(2.6) 2(2.8)	Dimensions must be in specification.
Surface Evaluation	To ensure the Ring may be attached properly. The surface must not have irregularities.	4(2.6) 3(2.8)	The surface must not have irregulartities.
Hardness of Ring	The Ring must resist	1(2.6)	The Ring must withstand minimum 5N

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Test	Purpose	Samples Tested†	Acceptance Criteria
Elana Catheter			
	deformation when a load is applied.	1(2.8)	of force when applied with stainless steel tweezers. The Ring must not have marks of tweezers on when forces are applied. The diameter at the point 0 force must be within specification.
Oval Load	The Ring must resist deformation when a load is applied.	2(2.6) 3(2.8)	The Ring must withstand 1N of force when pressure is applied in a way that could cause the Ring to become oval.
Bending due to Torque	The Ring must resist deformation when a load is applied.	3(2.6) 3(2.8)	The Ring must withstand 1N of force when pressure is applied in a way that could cause the Ring to bend.
Diameter Strength	The Ring must resist deformation when a load is applied.	2(2.6) 3(2.8)	Excessive force should be required when forces are applied to mis-shape the Ring when it is pushed down on a conical fitting.
Transport/Drop Test	The Ring must not be harmed if it is dropped while in the packaging	2(2.6) 2(2.8)	After being dropped 10 times from 1 meter height, the Ring dimensions must be within specification, and microscopic examination should find no deformities.

† Model number in parentheses, Model 2.6 or Model 2.8

MRI Compatibility:
Compatibility of the Elana Ring with MRI equipment was performed per ASTM (American Society for Testing and Materials) Standard numbers F2052-02, F2213-04, F2182-02a and F2119-01. Its labeling is in accordance with ASTM Standard F2503-05. Testing demonstrated that the device is MRI-Conditional in a static magnetic field of 3 Tesla or less, with spatial gradient magnetic field of 720 Gauss/cm or less and maximum MR system reported whole-body-averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of scanning.

B. Biocompatibility

Biocompatibility testing was performed on the Elana Arteriotomy System$_{HUD}$, i.e., the Elana Rings 2.6 & 2.8 and the Elana Catheter 2.0.

The Elana Rings were evaluated for biocompatibility as a permanent implantable device in direct contact with circulating blood in accordance with EN ISO 10993-1. Testing has been performed in accordance with FDA Good Laboratory Practices (GLP) and the appropriate ISO standards. The cytotoxicity (EN ISO 10993-5) and hemocompatibility (EN ISO 10993-4) tests were conducted on the Elana Rings 2.6 and 2.8 and the Rings passed the tests. The Elana Ring is 99.95% platinum, as confirmed by chemical analyses of the raw material including the identification and characterization of the trace elements. Platinum is known to be biocompatible, and is used in other neurovascular implants such as the Guglielmi Detachable Coil. Because of the inert nature of the metallic platinum and long history of its safe use in medical devices, additional biocompatibility tests such as irritation, sensitization, acute systemic toxicity, subchronic and chronic toxicity,

genotoxicity/carcinogenicity, and implantation tests were not conducted on the Elana Rings. Comprehensive application-specific animal experiments (acute and chronic) were performed in rabbits and pigs and no adverse effects were noted. In addition, in over 300 surgeries performed since 1993, no incidences of inflammatory responses or infection or other incompatibility reactions related to the Ring and its material have been reported in the operative and clinical records of the patients. The preclinical, prior history, and clinical data demonstrate that the Elana Rings are biocompatible for their intended use.

For identification and handling during operation, the Elana Rings 2.6 and 2.8 are provided with differently colored (White for Elana Ring 2.6 and Green for Elana Ring 2.8) loops of suture material. The suture material, Mersilene from Ethicon, Inc., complies with the requirements of the European Pharmacopoeia for sterile poly (ethylene terephthalate) suture and the Unites States Pharmacopeia for non absorbable surgical sutures. The extracts of the white and green handling loops were tested in cytotoxicity test. No cytotoxic effects were observed in presence of the extracts.

The Elana Catheter 2.0 is manufactured under contract by Spectranetics, Inc. and is identical in composite materials to the Spectranetics ClirPath Excimer Laser catheter cleared under K040067. In addition, the processes for manufacturing the Elana Catheter were selected based on the known toxicological, physical, and mechanical properties of the materials and processes currently used in the manufacture of the Spectranetics catheters. Biocompatibility testing was completed on the Spectranetics catheter, and the catheter passed all testing. As the Elana Catheter and the Spectranetics catheter have identical materials, nature of contact and contact duration, all required biocompatibility tests per ISO 10993-1 were not conducted on the Elana Catheter 2.0. Only limited biocompatibility testing (cytotoxicity and hemocompatibility) was performed and catheter passed the tests.

C. Pre-Clinical Animal Testing

The Elana Arteriotomy System$_{HUD}$ was tested in animal models to evaluate the safety of the system.

The following is a literature review of the *in vivo* studies conducted to date on the Elana Arteriotomy System$_{HUD}$.

- C.A.F. Tulleken et al. "Use of the Excimer Laser in High-Flow Bypass Surgery of the Brain." *J. Neurosurg* 78:477-480, 1993

  Background, Method and Results:
  The technique of laser-assisted anastomosis for high flow bypass surgery using the excimer laser is described in 15 rabbits and 1 patient. The left common carotid artery of the rabbits was excised and, with two anastomoses, connected to the right common carotid artery. An end-to-side anastomosis technique was used that obviated the temporary occlusion of the recipient artery. The end of the donor artery was connected for its circumference with

the exterior of the recipient artery and, with the aid of an excimer laser catheter (introduced via an artificial side branch of the donor artery), the wall of the recipient artery was evaporated. In two animals, occlusion of the anastomosis sites occurred. In the remaining 13 animals both anastomosis sites were patent by inspection at different times, followed by scanning electron microscopy in six animals.

In a patient with hypoperfusion of the brain caused by bilateral internal carotid artery occlusion, revascularization of the right hemisphere was obtained by placing a shunt between the proximal superficial temporal artery and the intracranial portion of the internal carotid artery, using a free transplant of the right inferior epigastric artery. The anastomosis with the internal carotid artery was created using the excimer laser-assisted technique without occlusion of the recipient artery.

- C.A.F. Tulleken et al. "The Modified Excimer Laser-Assisted High Flow Bypass Operation." *Surg Neurol* 46:424-429, 1996

  Background:
  To make high-flow revascularization of the brain possible, the author developed an anastomosis technique that obviates temporary occlusion of the recipient artery. After connecting donor and recipient vessels, an Excimer laser catheter, introduced by way of an artificial side branch, creates a hole at the anastomosis site. Because of the inconsistency of the diameter of the hole produced by the closed laser tip, we developed an extensive modification of this procedure.

  Methods:
  A new type of laser was developed, consisting of two layers of 60 μ laser fibers in a circular configuration with a diameter of 2.2 mm. The laser tip is fixed to the vessel wall at the anastomosis site by suction with a high-vacuum suction device, and a round piece of recipient vessel wall inside the anastomosis is cut out.

  Results:
  Using the aorta as the recipient vessel in 30 rabbits, the modified technique was developed and, in the end, produced anastomoses with a high patency rate. In 25 patients, high-flow bypasses for different indications were made using a venous transplant interposed between the external carotid artery or one of its branches and the intracranial internal carotid artery, utilizing the modified Excimer laser technique for the intracranial anastomosis. Complications related to the new anastomosis technique were minimal, and a satisfactory patency rate was obtained.

  Conclusions:
  The modified Excimer Laser-assisted anastomosis technique makes high-flow revascularization of the brain a safe procedure, since temporary occlusion of

the recipient proximal brain artery during the making of the anastomosis is obviated.

- CA Tulleken et al. "Non-occlusive excimer laser-assisted end-to-side anastomsis." *Ann Thor Surg* 63:S138-142, 1997

  Background:
  High-flow extracranial to intracranial bypass operation on the brain in a risky procedure because of the temporary occlusion of the intracranial portion of the internal carotid artery and thus, we developed a non-occlusive anastomosis technique in the experimental animal laboratory in 100 chronic and acute experiments in rabbits.

  Methods:
  In 40 patients we interposed a venous transplant between the external carotid artery or one of its branches and the intracranial portion of the internal carotid artery. During the construction of the distal anastomosis the recipient artery was not occluded. The donor vessel was stitched to the exterior of the recipient vessel and an Excimer laser catheter (MedolasGmbH, Amberg, Germany) was introduced by way of an artificial side branch. The tip of the laser catheter created a hole the wall of the recipient artery just inside the anastomosis. The cut-out full thickness portion of the recipient vessel wall remained attached to the tip of the laser catheter by way of high vacuum suction and was removed together with the laser catheter. Te artificial branch was occluded with a hemostatic clip. No interruption of blood flow in the recipient artery was induced during the making of the anastomosis.

  Results:
  The procedure was well tolerated by the patients and a high patency rate was observed.

  Conclusions:
  The nonocclusive Excimer laser assisted anastomosis technique is safe and yields a high long-term patency rate in neurosurgical patients. It cannot be excluded that there are indications for this method in coronary bypass surgery.

- J.F.C. Wolfs et al. "Scanning electron microscopic evaluation of nonocclusive excimer laser-assisted anastomosis in rabbits" *Acta Neurochir.* 142:1399-1407, 2000.

  Background:
  The nonocclusive Excimer laser assisted bypass technique has been described in previous studies and proved to be a promising bypass operation in vascular brain surgery. Little is known about the morphological regeneration process of the laser-assisted anastomosis in time. By way of a scanning electron microscopic study we examined the way in which we anastomosis site created by the nonocclusive Excimer laser-assisted anastomosis technique becomes endothelialized.

Methods:
In 14 rabbits the internal jugular vein was placed in a loop on the abdominal aorta. The distal anastomosis was made using the nonocclusive Excimer laser-assisted technique. The proximal anastomosis was made either laser-assisted or conventional end-to-side. After clipping of the aorta between the two anastomoses the vein served as a bypass. To evaluate the endothelialization at the laser-assisted anastomosis site in time, a scanning electron microscopic study was performed.

Results:
In the first hours after the bypass operation a new intimal surface is formed by fibrin and activated platelets. Some leukocytes are seen during the first days. The endothelialization process of the laser-assisted anastomosis site begins one day after the operation. The gradual endothelialization process evolved along two lines. First, endothelial cells grow from the side of the aorta to the bypass. Second, after one day solitary (blood-borne) endothelial cells deposit on the laser edge and the sutures, covering the platelet aggregates.

Conclusion:
The endothelialization of the Excimer laser-assisted anastomosis is more or less completed 9 days after the operation. The edge created by the laser becomes smoother after a few days and is gone for the most part after 9 days.

- H.J.N. Streefkerk et al. "Long-term reendothelialization of excimer laser-assisted nonocclusive anastomoses compared with conventionally sutured anastomoses in pigs." *J. Neurosurg.* 2005; 103(2): 328 – 336.

  Objective:
  In contrast to conventional anastomosis methods, the excimer laser-assisted nonocclusive anastomosis (ELANA) technique involves a platinum ring and intima-adventitia apposition with a rim of medial and adventitial layers exposed to the bloodstream. The authors assessed the reendothelialization of porcine carotid arteries through ELANA compared with conventional anastomosis by using scanning electron microscopy.

  Methods:
  In 28 pigs a bypass with one ELANA and one conventional anastomosis was made on the left common carotid artery. All patent anastomoses were evaluated intraoperatively with the aid of an ultrasonographic flowmeter and postoperatively by using scanning electron microscopy at 2 weeks, 2 months, 3 months, and 6 months thereafter. Twenty-four of 28 bypasses (48 of 56 end-to-side anastomoses) were fully patent at the time of evaluation. On scanning electron microscopic evaluation of the bypasses, all 48 patent anastomoses showed complete reendothelialization, including all 24 ELANAs in which the endothelium covered the rim and the laser-ablated edge completely. No endothelial difference was observed between conventional anastomoses and ELANAs, aside from the obvious anatomical differences like the platinum

ring, which had been completely covered with endothelium. At 6 months postsurgery, remodeling of the ELANA was observed, leaving the ring covered with a layer of endothelium as the narrowest part of the anastomosis.

Conclusions:
In long-term experiments, ELANA allows reendothelialization comparable to that achieved with conventional anastomosis. Considering its nonocclusive and high-flow characteristics, the ELANA technique is preferable in cerebral revascularization procedures

- Reinert M, et al. "Expanded polytetrafluoroethylene graft for bypass surgbery using the excimer laser-assisted nonocclusive anastomosis technique." *J Neurosurg.* 2006. 105: 758 – 764.

  Objective:
  Patients with complex craniocerebral pathophysiologies such as giant cerebral aneurysms, skull base tumors, and/or carotid artery occlusive disease are candidates for a revascularization procedure to augment or preserve cerebral blood flow. However, the brain is susceptible to ischemia, and therefore the excimer laser-assisted nonocclusive anastomosis (ELANA) technique has been developed to overcome temporary occlusion. Harvesting autologous vessels of reasonable quality, which is necessary for this technique, may at times be problematic or impossible due to the underlying systemic vascular disease. The use of artificial vessels is therefore an alternative graft for revascularization. Note, however, that it is unknown to what degree these grafts are subject to occlusion using the ELANA anastomosis technique. Therefore, the authors studied the ELANA technique in combination with an expanded polytetrafluoroethylene (ePTFE) graft.

  Method:
  The experimental surgeries involved bypassing the abdominal aorta in the rabbit. Ten rabbits were subjected to operations representing 20 ePTFE graft-ELANA end-to-side anastomoses. Intraoperative blood flow, followup angiograms, and long-term histological characteristics were assessed 75, 125, and 180 days postoperatively. Angiography results proved long-term patency of ePTFE grafts in all animals at all time points studied. Data from the histological analysis showed minimal intimal reaction at the anastomosis site up to 180 days postoperatively. Endothelialization of the ePTFE graft was progressive over time.

  Conclusions:
  The ELANA technique in combination with the ePTFE graft seems to have favorable attributes for end-to-side anastomoses and may be suitable for bypass procedures.

D. Packaging and Sterilization

The Elana Surgical Kit_{HUD} is packaged in a cardboard box, with the two components of the Elana Arteriotomy System individually packaged, together with a third individually packaged component, the Medela extension tubing.

The Elana Catheter is retained in a tray. The tray is then pouched in Tyvek/Polyester. The tray is then placed in a shelf carton. Both the outer pouch and the shelf carton have product labels attached. Validation of the packaging for the Elana Catheter shows a validity of 2 years. All packaging validation testing has been completed.

Each Elana Ring package contains a 2.6mm and a 2.8mm Ring on a suture loop in two separate cavities of a blister pack. The blister pack is sealed in a clear pouch, and placed in a shelf carton. The packaging for the Elana Ring has a validity of 5 years. All packaging validation testing has been completed.

The Elana Ring 2.6 & 2.8 are to be sterilized using Gamma radiation and the Elana Catheter 2.0 is to be sterilized using ethylene oxide (EtO) sterilization. The parameters for both processes will yield a minimum Sterility Assurance Level (SAL) of 10^{-6}. EtO residual levels for the Elana Catheter will be within the FDA guidelines (EtO $\leq$20mg, EC $\leq$12mg, EG $\leq$ 500ppm). Both the Elana Ring and the Elana Catheter have been tested for pyrogenicity and have been found to be non-pyrogenic. The devices will be labeled as non-pyrogenic, and lot-by-lot LAL testing will be performed. Sterilization validation for both devices has been completed.

E. Shelf Life

The shelf life testing for the Elana Catheter has been conducted for 1- and 4-years using accelerated and real-time aging tests. The packaging has been validated for 2 years and the Elana Catheter is labeled with a shelf life of 2 years from packaging.

The shelf life testing for the Elana Ring was for 5 years. The Elana Rings are labeled with a shelf life of 5 years from packaging. This 5-year shelf life testing is based on successful testing of the packaging for this period and the properties of the metal (minimal 99.95% platinum). This metal does not decay or corrode, so the useful life of the device is not limited.

XI. Summary of Clinical Information

The clinical information presented in support safety and probable benefit of the Elana Surgical Kit_{HUD} is comprised of two datasets, as follows:

1. Prospectively collected data from 7 centers in the United States and Europe ("IDE data"), namely Utrecht (The Netherlands), Berlin (Germany), Helsinki (Finland), New York (NY), Chicago (IL), Dallas (TX) and Little Rock (AR) under an IDE study. This dataset comprises 33subjects involving 37 device uses to date.

2. Retrospectively collected data from 7 centers in Europe ("EU data"): Utrecht (The Netherlands), Mannheim (Germany), Helsinki (Finland), Bern (Switzerland),

London (United Kingdom), Naples (Italy) and Göteborg (Sweden) from 1993 through 2006. This dataset comprises 330 subjects involving 375 device uses.

A. Prospective IDE Study

Study Overview

The objective of the prospective, non-randomized, international, multicenter IDE study is to confirm the clinical experience in Europe and demonstrate safety and efficacy of the Elana Surgical Kit_{HUD} in creating an intracranial arteriotomy in a nonocclusive manner.

Participating centers enroll subjects who require a temporary (protective bypasses that are required during surgery only) or permanent bypass to be connected to one or more unoccluded intracranial vessel(s) for an established indication and for whom the responsible surgeon feels they cannot be safely treated otherwise, e.g., because of a lesion not ideal for coiling or clipping or excision, or temporary or permanent occlusion of a vessel, without the temporary or permanent creation of a bypass. Subjects with a preoperative modified Rankin score of 4 or 5 were excluded. Subjects underwent a bypass surgery and received a bypass with the Elana Surgical Kit_{HUD} for at least one arteriotomy unless the bypass proves unnecessary during surgery or intra-operative exclusion criteria cause the subject to be excluded. Intra-operative exclusion criteria included no appropriately sized and viable arterial segment at a desired location for graft attachment can be approached, because all possible sites are unsuitable and the donor graft segment turns out not to be of suitable length and quality.

The primary endpoints of the IDE study are flow through the bypass graft and no device-related adverse events. Flow is judged by evaluating graft patency intra-operatively and at 7 (+/- 2) days follow-up for permanent bypasses, while only intraoperatively for temporary bypasses. The safety endpoint is the rate of mortality and non-fatal strokes at a 30 (+10/-3) day follow-up period. Neurological state and functional outcome using mRS at the 30 day follow-up visit are also evaluated for safety. Safety of Elana is compared to historically-derived information from the literature. Historical control is deemed appropriate because it can determine if graft bypasses created with the Elana Surgical Kit present the same type and incidence of adverse events typically seen in these procedures.

Subject Demographics

Enrollment began on August 3, 2007 with the 33rd subject enrolled on October 6, 2009]. The 33 subjects have all completed the 30 day post-bypass follow-up per protocol.

Currently, data are available on 33 subjects (32 subjects with a single Elana procedure and 1 subject with 2 Elana procedures). Table 5 depicts the demographics of the study subjects. Sixty-six per cent (66%) of the subjects were female and 53% of the subjects were over age 50. The vast majority of the subjects (91%) were treated for an aneurysm. Two subjects required temporary (protective) bypasses during surgery.

Table 5: IDE Study Demographics

	N (%) (Total N = 32)
Sex:	
Male	11 (34%)
Female	21 (66%)
Age (in years):	
< 18	1 (3%)
18-35	3 (9%)
36-50	11 (34%)
51-65	13 (41%)
>65	4 (13%)
Surgical Indication:	
Aneurysm	29 (91%)
Tumor	2 (6%)
Ischemia	1 (3%)

Results

Tables 6 and 7 below provide a summary of the outcomes for the 33 IDE subjects. The results in the table are distinguished by bypass procedures involving the anterior and posterior circulation because bypass procedures grafting to the posterior circulation (basilar artery, vertebral arteries, posterior cerebral arteries and posterior communicating arteries) carry a significantly higher risk of serious adverse events than those grafting to the anterior circulation.

The bypass patency rate at the end of surgery, for combined anterior and posterior circulation, is currently 94% and the bypass patency at 7 days post-operatively is 71% in the IDE study. To assess the safety of the Elana Surgical Kit_{HUD}, the clinical outcomes in Table 9 were analyzed to determine whether the subject benefited from the surgical intervention, i.e., whether mRS post-operatively (last recorded value) was equal to or better than the pre-operative mRS. Overall, 73% of the IDE subjects have equal or improved post-operative mRS (relative to their pre-operative mRS). The incidence of device related adverse events is 9%, the mortality rate is 9%, and the peri-operative non fatal stroke rate is 15%. Section VIII describes the adverse events in more detail.

Table 6: Primary Effectiveness Results for the IDE Study

Total Device Uses:	37
Total Subjects:	33 Anterior: 32/33 (97%) Posterior: 1/33 (3%)
Bypass patent at end surgery:	31/33 (94%) Anterior: 30/32 (94%) Posterior: 1/1 (100%)
Bypass patent at 7 days post-op [1,2]:	22/31 (71%) Anterior: 24/30 (73%) Posterior: 0/1 (0%)

[1] includes subjects that expired within 7 days (no patent bypass at 7 days)
[2] excluded 2 subjects with protective bypass

Table 7: Safety Results for the IDE Study

Total Device Uses	37
Total Subjects:	33 Anterior: 32/33 (97%) Posterior: 1/33 (3%)
All moderate/severe adverse events:	15/33 (45%) Anterior: 14/32 (44%) Posterior: 1/1 (100%)
Mortality:	3/33 (9%) Anterior: 2/32 (6%) Posterior: 1/1 (100%)
Non fatal stroke with permanent deficits at 30 days:	5/33 (15%) Anterior: 5/33 (16%) Posterior: 0/1 (0%)
mRs 30 days post-op the same as or lower then pre-op mRs	24/33 (73%) Anterior: 24/32 (75%) Posterior: 0/1 (0%)

B. Retrospective European Clinical Data

Clinical data was retrospectively collected on a total of 330 subjects, treated between 1993 and July 2006 using an experimental version of Elana Arteriotomy System in Europe [Utrecht (The Netherlands), Mannheim (Germany), Helsinki (Finland), Bern (Switzerland), London (United Kingdom), Naples (Italy) and Göteborg (Sweden)]. An independent reviewer/adjudicator has classified the adverse events of the ELANA surgeries of Dr.Tulleken in Utrecht for which post-operative mRS was higher than the pre-operative score to determine whether there had been a retained flap or unknown flap status and a complication occurred within two weeks post-operatively. This independent reviewer has also adjudicated all surgeries of Helsinki and Mannheim. Data analyzed included

bypass patency, mortality and non-fatal stroke rates. Ninety-three per cent (93%) of the subjects were followed for more than 30 days.

Patient Demographics (European Cohort)
Three hundred two (302) subjects (140 male, 162 female) were treated with the Elana device in Europe. A total of 375 Elana Arteriotomy Systems were used. Indications included aneurysm (216), ischemia (72), tumor (13), and ICA (internal carotid artery) malformation (1). Table 7 below depicts the demographics of the European subjects (330 subjects, 302 patients). Fifty four percent (54%) of the subjects were female and 60% of the subjects were over age 50. The majority of the subjects (72%) were treated for an aneurysm.

Table 8: Retrospective European (EU) Clinical Data Demographics

	N (%) (Total N = 302)
Sex:	
Male	140 (46%)
Female	162 (54%)
Age (in years):	
< 18	2 (0.6%)
18-35	26 (9%)
36-50	93 (31%)
51-65	136 (45%)
>65	45 (15%)
Surgical Indication:	
Aneurysm	216 (72%)
Tumor	13 (4%)
Ischemia	72 (24%)
Other	1 (0.3%)

Results
Tables 9 and 10 provide the results of the retrospectively collected EU data analysis. The results are stratified by bypass procedures involving the anterior and posterior circulation. The bypass patency rate at the end of surgery was 77%. The 7 day post-op bypass patency was not examined in the retrospectively collected EU experience. Overall, 72% of the EU subjects had equal or improved post-operative mRS relative to their pre-operative mRS. The incidence of all moderate to severe adverse events was 16%, the mortality rate was 7%, and the peri-operative non fatal stroke rate was 5 % in the EU data.

Table 9: Retrospective European (EU) Clinical Data Effectiveness Data

Total Device Uses:	375
Total Subjects:	330 Anterior: 307/330 (93%) Posterior: 23/330 (7%)
Bypass patent ≥ 0 days post-op:	255/330 (77%) Anterior: 235/307 (77%) Posterior: 20/23 (87%)

Table 10: Retrospective European (EU) Clinical Data Safety Data

Total Device Uses	375
Total Subjects:	330 Anterior: 307/330 (93%) Posterior: 23/330 (7%)
All moderate/severe adverse events:	52/330 (16%) Anterior: 38/307 (12%) Posterior: 14/23 (61%)
Mortality:	24/330 (7%) Anterior: 16/307 (5%) Posterior: 8/23 (21%)
Non fatal stroke:	17/330 (5%) Anterior: 12/307 (4%) Posterior: 5/23 (21%)
mRs 30 days post-op favorable†:	236/330 (72%) Anterior: 231/307 (75%) Posterior: 5/23 (22%)

† Varying from 0 days post-op to 2995 days post-op

Conclusions

The retrospective EU data do not raise any additional concerns that should further be investigated in the IDE study.

The EU data from 1993-2006 are still applicable today because the device and surgical technique have not changed.

C. Historical Data Comparison

Historical data were found via a literature study to identify conventional extracranial to intracranial (EC-IC) bypass operations to a major intracranial artery. The search focused on bypasses with vein grafts. Only series with at least 5 patients with vein grafts and those that presented safety data were included. No prospective study on conventional EC-IC bypass operations could be found. One publication (Amin-Hanjan et al., 2005) used population based methods to analyze a representative sample of the US medical community. The remaining articles present single-center retrospective experience. Only the Mayo clinic experience (Regli et al., 1995) analyzes a large series over a long period of time with operations by several surgeons and includes the initial learning curve. It provides the most reliable comparison for mortality and non fatal stroke. The data within this article fall within the range of the average from all other literature articles. Data on the mRS at 30 days post-op were not available for the literature cohort.

Table 11 compares the IDE data, the EU data and the Mayo clinic experience (Regli et al., 1995) literature article.

Table 11: Elana Arteriotomy System$_{HUD}$ Data versus Literature

Summary	**IDE data**	**EU data**	**Literature** (Regli et al., 1995)
Total device uses	37	375	n/a
Total subjects:	33	330	202
Anterior	32/33 (97%)	307/330 (93%)	104/202 (51%)
Posterior	1/33 (3%)	23/330 (7%)	98/202 (49%)
Bypass patent 0/7/30 days post-op:	7 days [1,2]:	≥ 0 days	30 days
Anterior	22/30 (73%)	235/307 (77%)	87/104 (83%)
Posterior	0/1 (0%)	20/23 (87%)	86/98 (88%)
Total	22/31 (71%)	255/330 (77%)	173/202 (86%)
Mortality:			
Anterior	2/32 (6%)	16/307 (5%)	11% (11/104)
Posterior	1/1 (100%)	8/23 (35%)	19% (19/98)
Total	3/33 (9%)	7% (24/330)	15% (30/201)
Non fatal stroke:	with permanent deficits at 30 days		
Anterior	5/32 (16%)	12/307 (4%)	Estimated[3] 13%
Posterior	0/1 (0%)	5/23 (22%)	Estimated[3] 23%
Total	5/33 (15%)	17/330 (5%)	Estimated[3] 18%

[1] includes subjects that expired within 7 days (no patent bypass at 7 days)

[2] excluded 2 subjects with protective bypass

[3] The Mayo Clinic experience [Regli et al, see footnote 8] includes 21 cases of neurological worsening due to early graft occlusion. The report does not report intra-operative stroke from other reasons. In 8/21 cases, the patients subsequently died, leaving 13 nonfatal strokes from graft occlusion. Other causes (thrombosis, hemorrhage) that also cause non-fatal strokes are fatal 1.8 times as frequent as graft occlusion. The assumption that hemorrhage and thrombosis cause nonfatal strokes in the same ratio as they caused fatal strokes thus leads to an estimated total of 36/201 (18%) non-fatal strokes. Along the same lines, non-fatal stroke for the posterior circulation should be responsible for about 63% of these strokes (for a rate of about 23%), and anterior circulation for the remainder for a rate of 13%.

Conclusions

The graft bypasses created with the Elana Arteriotomy Kit_{HUD} were shown to present the same type and incidence of adverse events (i.e., specifically mortality and non-fatal strokes) described for conventional bypass procedures presented in the literature (i.e., the Mayo clinic experience[2]). The incidence of mortality and peri-operative non-fatal stroke with permanent deficits were 9% and 7% respectively in the IDE study and 15% and 5% respectively in the European cohort. They are within those reported in the Mayo Clinic experience[2] where a mortality rate of 15% was reported and a non-fatal stroke rate of 18% was reported. Clinical data from the prospective IDE Study and the retrospective experience in Europe also show an acceptable incidence of adverse events. Based on mRS, the majority of the subjects also have an improved state of health after bypass surgery in both the IDE study and European cohorts. Additionally, in the IDE study, subjects were selected because the surgeon considered other treatment options, including conventional bypass with occlusion, unsafe. Thus, subjects treated in the IDE study might also be considered more vulnerable to ischemic events than the subjects selected in the literature.

XII. Risk/Probable Benefit Analysis

The clinical course is poor for an adult patient with an aneurysm or a skull base tumor affecting a large, intracranial artery that failed balloon test occlusion, that cannot be sacrificed, or that cannot be treated with conventional means due to local anatomy or complexity. When left untreated, patients with these lesions can reach morbidity and mortality rates of up to 50% in the first year after diagnosis (Langer, 2005). Bypass grafting to large intracranial arteries is a complex surgery, generally performed on patients with tumors and aneurysms involving the large feeding arteries of the brain, and the associated creation of a distal anastomosis using conventional bypass techniques carries the risk of severe complications related to temporary occlusion of the recipient artery and microvascular suturing. Particularly during temporary occlusion of the recipient artery, the patient is at high risk for ischemic stroke and peri-operative mortality. Non-fatal stroke can result in significant morbidity. Neurologic events may include deficits of various nerves, hemiparesis, hemiplegia, ataxia, loss of hearing or vision, and/or aphasia.

In conventional extracranial to intracranial (EC-IC) bypass operations, the surgeon must rapidly complete the microsuturing required for a vascular anastomosis while limiting the time of occlusion of the recipient artery. The advantage of the Elana Arteriotomy Kit_{HUD} is that it avoids temporary occlusion of the recipient artery. A risk associated with the Elana Arteriotomy Kit_{HUD} is the potential for the laser perforation of the vessel wall to be incomplete and result in a circular disk of tissue (or "flap") being retained on the artery wall. This condition may occur if the catheter does not completely contact the artery wall within the Ring or if the suture exerts uneven or excessive tension on the artery wall within the Ring. There is a potential for the retained flap to embolize when it is not removed manually and in order to remove the flap, the recipient artery still must be occluded.

Data have been provided for the Elana Arteriotomy Kit_{HUD} from an ongoing prospective IDE study as well as a retrospective cohort of European patients treated

with the Elana device. The graft bypasses created with the Elana Arteriotomy Kit_{HUD} were shown to present the same type and incidence of adverse events (i.e., specifically mortality and non-fatal strokes) reported for conventional bypass procedures in the publication literature discussing the Mayo clinic experience (Regli et al., 1995). The incidence of mortality and peri-operative non-fatal stroke with permanent deficits were 9% and 7% respectively in the IDE study and 15% and 5% respectively in the European cohort. This is within the rates reported in the Mayo Clinic experience where a mortality rate of 15% was reported and a non-fatal stroke rate of 18% was reported. Clinical data from the prospective IDE Study and the retrospective experience in Europe also show an acceptable incidence of adverse events. Based on mRS, the majority of the patients also have an improved state of health after bypass surgery in both the IDE study and European cohorts. Additionally, in the IDE study, patients were selected because the surgeon considered other treatment options, including conventional bypass with occlusion, unsafe. Thus, subjects treated in the IDE study might also be considered more vulnerable to ischemic events than the patients selected in the literature.

It should be noted that the safety of leaving a tissue flap in place with the Elana device has not been fully evaluated at this time due to the limited number cases where this has occurred. Elana has a requirement for physician training and has incorporated instructions into the labeling advising the surgeon to assess the flap and give consideration to its removal since there is a potential for a retained flap to embolize when not removed manually.

The population for which the Elana Arteriotomy System is indicated has a poor natural history and has in most cases no alternative treatment option. Hence, the collective evidence of the prospective IDE study data and the retrospective European data, as compared to the available literature data, demonstrate a reasonable assurance of safety and probable benefit for the indicated patient population.

XIII. Panel Recommendation

This HDE application was not taken to a meeting of the Neurological Devices Panel since it was determined that the preclinical and clinical issues raised by the HDE did not require panel review for the proposed device indication.

XIV. CDRH Recommendation / Decision

CDRH has determined that, based on the data submitted in the HDE, that the Elana Arteriotomy Kit_{HUD} will not expose patients to an unreasonable or significant risk or illness or injury, and the probable benefit to health from using the device outweighs the risks of illness or injury, and issued an approval order on March 10, 2011.

XV. Approval Specifications

Directions for use: See the Physician's Labeling.

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

Postapproval Requirements and Restrictions: See Approval Order.

XVI. References

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