CLINICAL SUMMARY

GENERAL INFORMATION

Device Trade Names:	DuraSeal Dural Sealant System
Applicant's Name and Address:	Confluent Surgical, Inc. 101A First Avenue Waltham, MA 02451

INDICATIONS FOR USE

The DuraSeal™ Dural Sealant System is intended for use as an adjunct to sutured dural repair during cranial surgery to provide watertight closure.

DEVICE DESCRIPTION

The DuraSeal Dural Sealant System consists of components for preparation of an absorbable poly (ethylene glycol) hydrogel sealant and a delivery system (i.e., applicator, spray tips and plunger cap) packaged in a sterile single use kit. The hydrogel sealant is specifically intended for use as an adjunct to sutured dural repair during cranial surgery to provide watertight closure.

The sealant is composed of two solutions, a polyethylene glycol (PEG) ester solution and a trilysine amine solution (referred to as the "blue" and "clear" precursors, respectively). When mixed together, the precursors provide rapid *in-situ* polymerization to form a biocompatible absorbable hydrogel suitable for sealing the dura mater. No external energy requirements, such as a light or heat source, are required to initiate the reaction. There is very little or no heat evolution during the polymerization reaction, which occurs within seconds (when this hydrogel is applied to the palm of a hand there is no noticeable heat generated).

The mixing of the precursors is accomplished in the DuraSeal delivery system as the materials exit the tip of the delivery system. The delivery system allows a conformal coating that has excellent tissue adherence primarily through the mechanism of mechanical interlocking of the hydrogel with the tissue surfaces. The mixing provided by the delivery system also ensures a complete reaction of the precursors.

The cross linked solid hydrogel is more than 90% water at application. Due to this high water content, the hydrogel has physical properties similar to tissue. The net result is that an effective absorbable barrier is formed that is tissue compliant, tissue adherent, and lubricious. The hydrogel implant is absorbed in approximately 4 to 8 weeks, sufficient time to allow for healing. The breakdown products are readily cleared from the body, primarily through the kidneys.

The DuraSeal Dural Sealant can be used for up to one hour following reconstitution.

CONTRAINDICATIONS

- Do not apply the DuraSeal Dural Sealant System to confined bony structures where nerves are present since neural compression may results due to hydrogel swelling. The hydrogel may swell up to 50% of its size in any dimension.

WARNINGS AND PRECAUTIONS

WARNINGS:

- The safety and performance of the DuraSeal hydrogel has not been established:
  - In patients with a known allergy to FD&C Blue #1 dye.
  - In patients undergoing a cranial procedure that involves penetration (other than superficial) of the air sinus or mastoid air cells.
  - In patients with severely altered renal or hepatic function.
  - In combination with other sealants or hemostatic agents.
  - In patients with a compromised immune system or autoimmune disease.
- Do not use if an active infection is present at the surgical site.

PRECAUTIONS:

- Use only with the delivery system provided with the polymer kit.
- The DuraSeal Dural Sealant System is provided sterile. Do not use if packaging or seal has been damaged or opened. Do not re-sterilize.
- The DuraSeal Dural Sealant System is intended for single patient use only. Discard opened and unused product.
- Do not use if the PEG powder is not free flowing.
- Use within 1 hour of preparation of the blue precursor.
- Prior to application of the DuraSeal Dural Sealant System, ensure that complete hemostasis has been achieved.
- Incidental application of DuraSeal hydrogel to tissue planes that will be subsequently approximated, such as muscle and skin, should be avoided.
- Use in patients with surgical wound classification Class I/Clean, where the linear extent of the durotomy is at least 2 cm, and where the dural margin from the edges of the bony defect is at least 3 mm throughout.
- The safety and performance of the DuraSeal hydrogel has not been established:
  - In persons younger than 18 years of age.
  - In procedures involving petrous bone drilling.

ALTERNATIVE PRACTICES AND PROCEDURES

The current methods of dural repair consist of the direct application of interrupted sutures, possibly with the use of dural replacement materials (i.e., duraplasty) to cover significant dural gaps. Adjunct dural repair techniques used today entail the local application of biological adhesives (i.e., homologous or autologous fibrin sealants), application of absorbable gelatin or collagen sponge, autologous muscle, temporalis fascia, fascia lata, pericranium, ligamentum nuchae, fat grafts, or cyanoacrylate glue. While these methods are useful in situations where the deficit of dura exists, it is often still not possible to achieve a watertight closure and currently there are no commercially available products specifically indicated as an adjunct to seal smaller dural openings.

Use of fibrin sealants of various types has gained in popularity for dural sealing and management of CSF leaks, but has had variable results. Several studies have demonstrated the effectiveness of fibrin sealants for prevention of CSF leaks in cranial patients; however, there are also studies that have shown the use of fibrin glue to be no more effective than the application of autologous tissue in preventing postoperative CSF leakage, or the use of no adjunct technique.

MARKETING HISTORY

The DuraSeal Dural Sealant System is approved for commercial sale in the European Economic Area (EEA) since June 2003 (CE Mark), in South Africa since January 2004, in the United Arab Emirates since March 2004, and in Australia since August 2004

The DuraSeal System has not been withdrawn in any country due to reasons related to safety and effectiveness of the device.

POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential Adverse Events

All surgical procedures are associated with a level of risk. A common risk associated with an incision in the brain tissue is CSF leak, which may result in development of meningitis. Other potential complications that may result from a CSF leak in the head include inflammation of the area adjacent to the leak, severe headaches, low pressure inside the brain from loss of fluid, damage to the nerve roots, decreased function of the nervous system, collections of fluid in the brain compartments, and the formation of fluid-filled cysts.

DuraSeal Sealant is naturally dissolved within the body during approximately 4 to 8 weeks after its application. Potential risks and adverse events that could occur from the use of the DuraSeal Dural Sealant System include, but are not limited to, wound infection, immediate, delayed and/or persistent CSF leak, renal compromise, inflammatory reaction, neurological compromise, allergic reaction and/or delayed healing.

Observed Adverse Events

The DuraSeal Dural Sealant System was evaluated in 111 investigational patients in the pivotal clinical study.

Table 1 presents Adverse Events observed in these patients. Any adverse events occurring at a rate of 1% or higher are listed.

Adverse event rates presented are based on the number of patients having at least one occurrence of a particular adverse event divided by the total number of patients treated.

Table 1

Adverse Events

Adverse Event Category	# of events	# of patients*	
		n	%
General Events			
Bleeding	4	4	(3.6)
Dermatologic Events	11	11	(9.1)
Dizziness	9	8	(7.2)
Edema (non-systemic)	20	19	(17.1)
Fever Post-op (>38.5°C for 48 hours)	6	6	(5.4)
Fever (<38.5°C for <48 hours)	5	5	(4.5)
General Malaise	9	9	(8.1)
Headache (responding to standard therapy)	9	9	(8.1)
Infection (non-incisional) (e.g. thrush, otitis media, keratitis, catheter-related infection)	10	8	(7.2)
Musculoskeletal Events	22	21	(18.9)
Nausea and/or Vomiting	29	24	(21.6)
Other: Corneal abrasion, chemotherapy complication, hiccoughs	3	3	(2.7)
Surgical Wound Complications			
Deep Surgical Site Infection	9	8	(7.2)
Late (>30 days) Wound Infection	3	3	(2.7)
Pain, Incisional	2	2	(1.8)
Wound erythematic/inflammation	2	2	(1.8)
Cardiovascular Events			
Hypertension	5	5	(4.5)
Arrhythmia	6	6	(5.4)
Peripheral edema	2	2	(1.8)
Abdominal/Hemic/Lymphatic Events			
Electrolyte Imbalance	17	11	(9.9)
Elevated Liver Enzymes	16	11	(9.9)
GI Disturbance	21	16	(14.4)
Hematologic Abnormality	10	7	(6.3)
Respiratory/Pulmonary Events			
Respiratory Difficulties	7	6	(5.4)

Table 1

Adverse Events

Adverse Event Category	# of events	# of patients*	
		n	%
Upper Respiratory/Bronchial Infection	4	4	(3.6)
Pneumonia	3	3	(2.7)
Urogenital Events			
Urinary Tract Infection	11	11	(9.9)
Urinary Difficulty	9	9	(8.1)
Ureterolilithiasis	2	2	(1.8)
Other	2	2	(1.8)
Central Nervous System Events			
Cerebral Edema	4	4	(3.6)
CSF Leak (protocol definition)	5	5	(4.5)
Stroke/CVA/Cerebral Hemorrhage	7	5	(4.5)
Headache: not responding to standard medications	6	5	(4.5)
Hydrocephalus	4	4	(3.6)
Meningitis (Aseptic)	5	5	(4.5)
Meningitis (Bacterial)	2	2	(1.8)
Neurological Symptoms			
-Cognitive	6	5	(4.5)
-Cranial nerve deficit	49	34	(30.0)
-Motor deficit	19	17	(15.3)
-Neuropsychiatric disorders	7	7	(6.3)
-Speech difficulty	11	10	(9.0)
-Visual disturbance	25	22	(19.8)
Pseudomeningocele (responding to conservative therapy)	2	2	(1.8)
Seizure	3	3	(2.7)
Subdural Hematoma	2	2	(1.8)

*Patients can have more than one adverse event and in more than one category.

The incidence and nature of adverse events observed in this patient population are consistent with the type and complexity of the surgery performed and the co-morbid state of the treated patients. There were no unanticipated adverse device effects. There were two patient deaths (out-of-hospital). In both cases, the deaths were attributed to the patients' prior condition.

The DuraSeal Dural Sealant System was also clinically evaluated in an additional 47 patients during a European Pilot Trial. The nature and severity of events reported in this study were consistent with the results presented in **Table 1**.

SUMMARY OF PRE-CLINICAL STUDIES

Biocompatibility

Confluent Surgical has performed biocompatibility testing that evaluates the device as one system. All hydrogel samples evaluated in biocompatibility tests were prepared using the kit components supplied, in accordance with the Instructions for Use. Additional studies have evaluated the DuraSeal delivery system (i.e., applicator, spray tips and plunger cap).

Biocompatibility testing (reference **Table 2**) of the formed DuraSeal hydrogel has been performed consistent with Federal Good Laboratory Practices Regulations (21 CFR § 58) and FDA's Blue Book memorandum G95-1 "Use of ISO-10993 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing". This document defines the DuraSeal hydrogel as a tissue/bone contacting implant of permanent contact duration. Additionally, in vitro proliferative effects of the DuraSeal hydrogel in various human cancer cell lines was evaluated. The DuraSeal hydrogel met the requirements for all tests performed, and was deemed to have no anti- or proliferative effects.

Table 2 Summary of DuraSeal Sealant Biocompatibility

Test Reference	Method Reference	Results
Cytotoxicity (Agarose Overlay Method)	International Organization for Standardization: Biological Evaluation Medical Devices, Part 5. 10993-5: *Tests for Cytotoxicity*	Non cytotoxic
ISO Maximization Sensitization Study (Guinea Pigs)	International Organization for Standardization: Biological Evaluation Medical Devices, Part 10. 10993-10: *Tests for Irritation and Sensitization*	Non sensitizing
ISO Modified Intracutaneous Study	International Organization for Standardization: Biological Evaluation Medical Devices, Part 10. 10993-10: *Tests for Irritation and Sensitization*	No evidence of significant irritation.
USP and ISO Modified Systemic Toxicity	International Organization for Standardization: Biological Evaluation Medical Devices, Part 11. 10993-11: *Tests for Systemic Toxicity*	No mortality or systemic toxicity
USP Pyrogenicity	International Organization for Standardization: Biological Evaluation Medical Devices, Part 11. 10993-11: *Tests for Systemic Toxicity*	Nonpyrogenic
Subchronic toxicity	This test evaluates the potential systemic toxicity of the test material following implantation in the rat.	No Systemic Toxicity
Bacterial Reverse Mutation Assay	International Organization for Standardization: Biological Evaluation Medical Devices, Part 3. 10993-3: *Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity*	Non mutagenic
In Vitro Mammalian Chromosome Aberration Test	*In vitro* Chromosomal Aberrations Test evaluates the potential clastogenic properties of a test material solution.	Non mutagenic

Test Reference	Method Reference	Results
Micronucleus Cytogenic Assay in Mice	International Organization for Standardization: Biological Evaluation Medical Devices, Part 3. 10993-3: *Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity*	No clastogenic activity
In Vitro Mammalian Cell Gene Mutation Test	International Organization for Standardization: Biological Evaluation Medical Devices, Part 3. 10993-3: *Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity*	Non mutagenic
ISO Muscle Implantation Study (2 Weeks)	International Organization for Standardization: Biological Evaluation Medical Devices, Part 6. 10993-6: *Tests for Local Effects after Implantation*	Slight Irritant
ISO Subcutaneous Implantation Study in the Rat (10 days)	International Organization for Standardization: Biological Evaluation Medical Devices, Part 6. 10993-6: *Tests for Local Effects after Implantation*	No significant macroscopic reaction. Microscopically material classified as non-irritant.
In Vitro Hemolysis (Modified ASTM-Direct Contact Method)	International Organization for Standardization: Biological Evaluation Medical Devices, Part 4. 10993-4: *Selection of Tests for Interactions with Blood*	Nonhemolytic
In Vitro Proliferative Effects of DuraSeal in Various Human Cancer Cell Lines	This test determines whether DuraSeal impacts the in vitro cancer cell growth (pro- or anti-proliferative effects) of 4 human cancer cell lines, HT29 Colon Cancer, OVCAR3 Ovarian Cancer, A549 Lung Cancer, and U-87 MG Gliobastoma. Cells were exposed to the test article for four days, after which time cell proliferation was assessed.	No proliferative or anti-proliferative effect.

Animal Testing

Confluent Surgical has conducted a series of animal studies to evaluate the *in vivo* performance and safety of the DuraSeal Dural Sealant System. **Table 3** provides a summary of the tests performed and the relevant findings.

Table 3 Summary of Animal Studies

Test Performed	# Animals/ Study Duration	Summary/Relevant Findings
Canine Cranial Sealing Study	13 test and 13 control/56 days	Study performed to demonstrate both safety and effectiveness of the DuraSeal Sealant in a canine cranial durotomy model. Study endpoints included sealing capability of CSF leaks after treatment with DuraSeal when compared with control following challenge with a Valsalva maneuver, and confirmation of normal healing (tolerance) following application of the DuraSeal Sealant. Animals were observed to qualitatively assess normal behavior, general health signs (e.g., incision healing, appetite), and for possible CNS abnormalities. At 1, 4, 7, and 56 days post treatment, three canines from both the DuraSeal treated and the control group were terminated. A Terminal Pressure Test was conducted using a mechanical ventilator to perform a Valsalva maneuver up to a pressure of 55 cm H_20. The results obtained from this controlled study suggest that the DuraSeal is effective as a tissue sealant to achieve optimal dural closure and repair, and that the hydrogel material is well tolerated.

Test Performed	# Animals/ Study Duration	Summary/Relevant Findings
DuraSeal MR and CT Imaging Evaluation: Canine Craniotomy Model	2 test/14 weeks	An evaluation was undertaken to determine the MR and CT imaging characteristics of the DuraSeal Sealant following implantation. Additionally, histological evaluation was performed to evaluate for potential local toxicity and/or space filling defect. Following a craniotomy in two canines, DuraSeal was sprayed onto the dura, and the bone flap was then replaced. Following recovery, both animals underwent MR and CT imaging at 3 days and at 2, 4, 6, 8, and 10 weeks post-treatment. Gel appearance at each time point was characterized. Histological analysis was performed 14 weeks following implantation. Both dogs remained neurologically intact. DuraSeal Sealant was readily apparent with all imaging techniques out through 6 weeks. Absorption of the hydrogel and subsequent closure of the remaining void was documented. Histopathology showed minimal changes, with excellent tissue compatibility of the gel. Histological examination found an unremarkable response with no neurotoxicity, or space-filling defect.
Rat Brain Parenchymal Implant Study	8 test and 8 control/42 days	The DuraSeal Sealant was evaluated for the potential to cause local irritation or toxicity at the implant site. Micro forceps were used to implant pieces of DuraSeal into brain parenchyma in test animals, and to create sham injuries in controls. Examinations for clinical signs of disease or abnormality and a neurological assessment were conducted prior to treatment, and at days 4, 14, 28, and 42 post-treatment. At days 4 and 42 after implantation, four animals per treatment group were euthanized. The brain and proximal portion of the cervical spinal cord were dissected and removed. No neurologic deficits were noted and no adverse reactions were observed for any of the test sites at explant. There was no evidence of a local effect or a neurotoxicity effect in association with the test article implanted within the neuropil of the brain in rats.
Study in the Rat Following Injection of Test Extracts into the Brain	13 test and 13 control/2 weeks	The potential neurotoxicity of the DuraSeal Sealant compared to a control solution was evaluated following injection of prepared extracts into the lateral ventricle and the cisterna magna of the brain of a rat. Detailed health examinations and neurologic assessments were conducted at prespecified intervals. At 4 days and 2 weeks following injection, half of the animals from each cannulation type and treatment group were euthanized and necropsy performed. No macroscopic encapsulation was observed at any test or control cannulation site. The microscopic evaluation of the tissues revealed no evidence of a treatment related response. Under the conditions of the study, there was no significant evidence of neurotoxicity from the test extract injected into the brain of rats.
Evaluation of DuraSeal Persistence Following Subcutaneous Implantation in the Rat	21 test and 21 control/14 weeks	Study performed to evaluate the in-vivo persistence and degradation of the DuraSeal Sealant over a period of 14 weeks following subcutaneous implantation in the rat. Results demonstrate that the DuraSeal hydrogel sealant persists essentially in its initial form for 2 weeks, becomes noticeably softer at 4 weeks and is predominantly degraded by 6 weeks. Degradation was complete within 8 weeks of implant.
Study for Effects on Embryo-Fetal Development with DuraSeal in Rats Following Intraperitoneal Administration	25 test and 25 control/2 weeks	Study performed to determine the developmental toxicity, including the teratogenic potential of the DuraSeal Sealant in rats following subcutaneous administration on Day 6 of gestation. Detailed clinical observations were performed daily up through 20 days of gestation. Dams were subjected to necropsy including uterine examination and fetuses were evaluated for malformations and developmental variations. No toxic or teratogenic observations were noted comparing DuraSeal to a control substance. Based on the results of this study, the No Observable Effect Level (NOEL) for maternal and developmental effects is >0.1mL (0.3909 mL/kg) of DuraSeal, which represents almost 5.5 times the anticipated exposure under normal conditions of use. Under the conditions of this study, the DuraSeal sealant was found to be non-teratogenic in rats.

Sterilization

E-beam irradiation sterilization validated in accordance with "*Sterilization of health care products – Requirements for validation and routine control – Radiation sterilization"*, ANSI/AAMI/ISO 11137 – 1994 and "*Sterilization of medical devices – Validation and routine control sterilization by irradiation",* EN552.

Shelf Life

A 6-month shelf life was established based on both accelerated and real-time aging studies.

In Vitro Product Testing

A series of *in vitro* tests were performed on the components and materials of the DuraSeal System (final, finished, sterilized devices). These tests were performed to assure that the device performed as expected, and that the components are safe to use in the prescribed manner. In addition to the studies identified in **Table 4**, environmental testing was performed to assure that the product is not affected by temperature extremes or maximum irradiation dose.

Table 4 In Vitro Product Testing

Design Characteristic	Test Description	Results
Gel Time and Pot Life	Test evaluates the time it takes for a hydrogel to form when the two precursor components are brought into contact with each other immediately (gel time) and 1 hour (pot life) following reconstitution of the blue precursor.	Upon mixing precursors, a gel is formed in ≤ 3.5 seconds.
Swelling	Evaluates the percent weight gain resulting from 24-hour immersion in 37°C phosphate buffered solution.	In vitro swelling is ≤ 200%.
In vitro absorption - disappearance	Hydrogel must be visibly dissolved when placed in a phosphate buffered solution.	DuraSeal hydrogel shall be visibly dissolved in 1.2 to 4 days after immersion into the phosphate buffered solution, pH of 7.4 at 60.4°C.
Gel application-pressure integrity	Test evaluates the mechanical joints of the applicator to ensure that the device is sufficiently robust to withstand anticipated use.	Applicators did not leak or fail when pressurized to 68 psi for a minimum of 4 seconds.

Design Characteristic	Test Description	Results
Uniform gel application	Evaluates proper function of the applicator and mixing of the precursors to the target area to assure uniform sealant application.	Applicator disperses gel in a pattern < 10mm diameter when Spray Tip is 2-4cm from target tissue.

SUMMARY OF CLINICAL STUDIES

US Pivotal Trial

A prospective, multi-center, non-randomized, single arm clinical investigation to evaluate the safety and effectiveness of the DuraSeal Dural Sealant System as an adjunct to sutured dural repair during cranial surgery to provide watertight closure was initiated in June 2003, pursuant to FDA's approval of IDE G030035. The study involved 10 investigational sites within the United States and 1 site in Europe. A total of 111 patients were treated with the DuraSeal Sealant.

Inclusion criteria:

Pre-Operative Inclusion Criteria

Patients had to meet the following criteria to be eligible for participation in the study:

- Patient is between 18 and 75 years of age
- Patient is scheduled for an elective cranial procedure that entails a dural incision using any of the following approaches (or combination): Frontal, Temporal, Parietal, Occipital and/or Suboccipital
- Patient requires a procedure involving surgical wound classification Class I/Clean
- Patient, or authorized representative, signs a written Informed Consent form to participate in the study, prior to any study mandated determinations or procedures

Intra-Operative Inclusion Criteria

Patients had to meet all of the following intra-operative inclusion criteria to be eligible for treatment with the DuraSeal System:

- Surgical wound classification Class I/Clean
- Linear extent of durotomy is at least 2 cm
- Dural margin from edges of bony defect is at least 3 mm throughout
- Patient must have a CSF leak after primary dural closure, either spontaneous or upon Valsalva maneuver, up to 20 cm H_2O for 5-10 seconds

Exclusion criteria:

Pre-Operative Exclusion Criteria

Exclusion criteria were intended primarily to deny entry to patients that might be severely immunocompromised, possibly predisposing the patient to infection or delayed healing; or patients with neurological symptoms and other pre-existing conditions that could confound analysis of study results. Those exclusion criteria were as follows:

- Patient requires a procedure involving translabyrinthine, transsphenoidal, transoral and/or any procedure that penetrates the air sinus or mastoid air cells; superficial penetration of air cells are not excluded
- Patient has had a prior intracranial neurosurgical procedure in the same anatomical location
- Patient has had chemotherapy treatment within 6 months prior to, or planned during the study (until completion of last follow-up evaluation)
- Patient has had prior radiation treatment to the surgical site or planned radiation therapy within one month post procedure
- Patient has hydrocephalus (e.g. elevated intracranial pressure > 22 cm H_2O)
- Patient has a known malignancy or another condition with prognosis shorter than 6 months (patients with stable systemic disease can be included, extent of disease will be documented)
- Patient has pre-existing external ventricular drainage or lumbar CSF drain
- Patient is not able to tolerate multiple Valsalva maneuvers or an intra-operative CSF shunt does not allow for transient elevation of CSF pressure during Valsalva maneuvers
- Patient has a systemic infection (e.g. UTI, active pneumonia) or evidence of any surgical site infection (superficial, deep, or organ space), as determined by fever > 101°F, WBC > 11,000/uL, positive blood culture, positive urine culture, and/or by a positive chest x-ray.
- Patient has a known allergy (or history of intolerance) to FD&C Blue #1 dye
- Pregnant or breast-feeding females or females who wish to become pregnant during the length of study participation
- Patient has traumatic injuries to the head
- Patient has been treated with chronic steroid therapy unless discontinued more than 6 weeks prior to surgery (standard acute perioperative steroids are permitted)
- Patient has a compromised immune system or autoimmune disease (WBC count less than 4000/uL or greater than 20,000/uL)
- Patient is not likely to comply with the follow-up evaluation schedule
- Patient with uncontrolled diabetes, as determined by two or more incidences of elevated blood sugar levels (fasting glucose >120mg/dL) within the 6 months prior to surgery
- Patient with creatinine levels > 2.0 mg/dL
- Patient with total bilirubin > 2.5 mg/dL
- Patient has a clinically significant coagulopathy with a PTT > 35, INR > 1.2, receiving aspirin, non-steroidal anti-inflammatory agents
- Patient is receiving warfarin or heparin (including analogs)
- Patient is participating in a clinical trial of another investigational drug or device

Intra-Operative Exclusion Criteria

Patients who meet any of the following intra-operative exclusion criteria were to be considered screening failures and were not eligible to be treated with the DuraSeal System:

- Incidental finding of any of the Pre-operative Exclusion Criteria
- Patient required use of synthetic or non-autologous duraplasty material
- Patient has a gap greater than 2 mm remaining after primary dural closure

Safety and Efficacy Parameters

The primary efficacy endpoint is the percent (%) success in the treatment of intra-operative CSF leakage following DuraSeal Sealant application and is defined as:

- *Success* = No CSF leakage from dural repair intra-operatively after up to two DuraSeal Sealant applications, during Valsalva maneuver up to 20 cm H_20 for 5 to 10 seconds.
- *Failure* = CSF leakage from dural repair intra-operatively after up to two DuraSeal Sealant applications, during Valsalva maneuver up to 20 cm H_20 for 5 to10 seconds.

Safety endpoints include the incidence of CSF leaks within 3 months of the index procedure as determined from clinical diagnosis by one of the following methods:

- CSF leak or pseudomeningocele related surgical intervention (i.e., breaking skin) within 3 months post-op; or
- CSF leak confirmation by diagnostic testing within 3 months post-op; or
- CSF leak confirmation by clinical evaluation including physical examination of the surgical site within 3 months post-op.

Additional safety endpoints include the incidence of adverse events and adverse device-related adverse events diagnosed by physical examination, protocol-specified diagnostic laboratory tests, neurological assessments (including pain and modified Rankin Scale) and CT imaging assessment performed by independent radiologists for evaluation of extradural collections and adverse findings.

Prior to initiation of enrollment, all study neurosurgeons were trained on the proper use of the DuraSeal Dural Sealant System. Patients requiring elective cranial surgery were screened for eligibility based on pre-operative eligibility criteria and were treated with the DuraSeal Dural Sealant System only if specific intra-operative criteria were met. Patients who did not meet the intra-operative eligibility criteria were considered screening failures and withdrawn from the study without additional follow-up. Treated patients were evaluated at discharge or within 7-day post procedure, 6-weeks and 3-months post procedure.

The Investigator conducted the appropriate cranial procedure according to the standard procedures and practices at the institution and the sutured dural repair was completed to the Investigator's satisfaction. If necessary, autologous grafts were harvested to augment dural closure. Upon completion of the sutured dural repair, the closure was evaluated for cerebrospinal fluid (CSF) leakage with a baseline Valsalva maneuver to 20 cm H_2O. If a spontaneous leak was already apparent immediately after dural closure, no Valsalva was performed. If a leak was present, either spontaneously or upon Valsalva, the Dural Sealant was applied to the closure site and a subsequent Valsalva maneuver was conducted to evaluate the effectiveness of the device to hold a watertight seal.

Patients were clinically assessed for the primary efficacy endpoint and safety endpoints throughout the duration of the trial. CT scans were performed at baseline, at discharge or within 7-days post-procedure and at 3 months post-procedure and reviewed by independent neuroradiologists for an evaluation of extradural measurements and unexpected findings.

Patient Accountability and Demographics:

The study involved 10 investigational sites within the United States and 1 site in Europe. A total of 111 patients were enrolled in the study and treated with the DuraSeal Dural Sealant System. Of those, 107 patients (>96%) completed the three-month follow-up.

Of the patients that did not complete the study, two (2) patients were determined to be lost-to-follow-up following the 6-week visit, despite repeated attempts to locate the patients. Additionally, two patients died during the study follow-up period. The deaths were unrelated to the study treatment.

For the majority of the evaluation time points, the follow-up rate was 98% or greater. With the exception of the two patients lost-to follow-up and the 2 patient deaths, only one patient missed the 6-week follow-up visit and no patients missed the 3-month follow-up visit.

Table 5 Subject Demographics

Characteristic	*DuraSeal Study Population*
N	111
Men/Women	35/76
Age (range)	49.3 ± 13.2 (20-75)
Height (cm)	169.5 ± 10.6 (152-199)
Weight (kg)	80.5 ± 23.0 (45.0-202.8)
Current Smoker	
Never	52 (46.8%)
History	26 (23.4%)
Yes	33 (29.7%)
ASA* Scores (n, %)	
I	14 (12.6%)
II	59 (53.2%)
III	36 (32.4%)
IV	1 (0.9%)
*American Society of Anesthesia	
Indication for Surgery:	
AVM	7 (6.3%)
Aneurysm	12 (10.8%)
Chiari Malformation	6 (5.4%)
Cyst	3 (2.7%)
Epilepsy	10 (9.0%)
Nerve Decompression	21 (18.9%)
Tumor	51 (45.9%)
Acoustic Neuroma	6
Cerebellopontine angle	5
Dermoid/Epidermoid	2
Frontal	5
Meningioma	12
Parietal/parietotemporal/temporal	9
Other **	12
Incidental right posterior artery communicating artery stenosis	1 (0.9%)
**includes brain/brainstem, cavernous sinus, intraventricular/ventricular tumors, occipital metastasis, chordoma and medullobastoma	

A poolability analysis was performed to ensure that data across all sites could be combined for analysis. "Site" was not found predictive for key safety variables and no variability among sites was seen with respect to the primary endpoint, intraoperative sealing success.

Efficacy Analyses

The primary endpoint for this study is the percent (%) success in the treatment of intraoperative CSF leakage following DuraSeal sealant application defined as no CSF leakage from dural repair intra-operatively after up to two DuraSeal Sealant applications during Valsalva maneuver up to 20 cm H_2O for 5 to 10 seconds.

All 111 patients treated with the DuraSeal Sealant showed no leakage during the intra-operative assessment. Of the 111 patients treated, two (2) patients were considered not evaluable for purposes of the primary efficacy analysis, as the pressure applied during the post-treatment Valsalva maneuver only reached 10 cm H_2O.

Two primary efficacy analyses were performed:

- Intent to Treat Population (n = 111): The remaining 109 patients (98.2%) were primary endpoint successes. The 95% confidence interval for the true percent of successes is 93.6% to 99.8%.
- Per Protocol Population (n = 109): All 109 patients (100%) were primary endpoint successes. The 95% confidence interval for the true percent of successes is 96.7% to 100%.

The goal of this study was to demonstrate that the two-sided 95% confidence limit around the primary endpoint success event rate (expected to be at least 90%) is greater than a minimally clinically acceptable success rate of and Objective Performance Criteria (OPC) defined to be 80%.

For both the Intent to Treat and Per Protocol analyses, the lower limit of the observed confidence interval is greater than 80%, the minimally clinical acceptable success rate. Therefore, the success criterion for this study has been satisfied.

Safety Evaluations

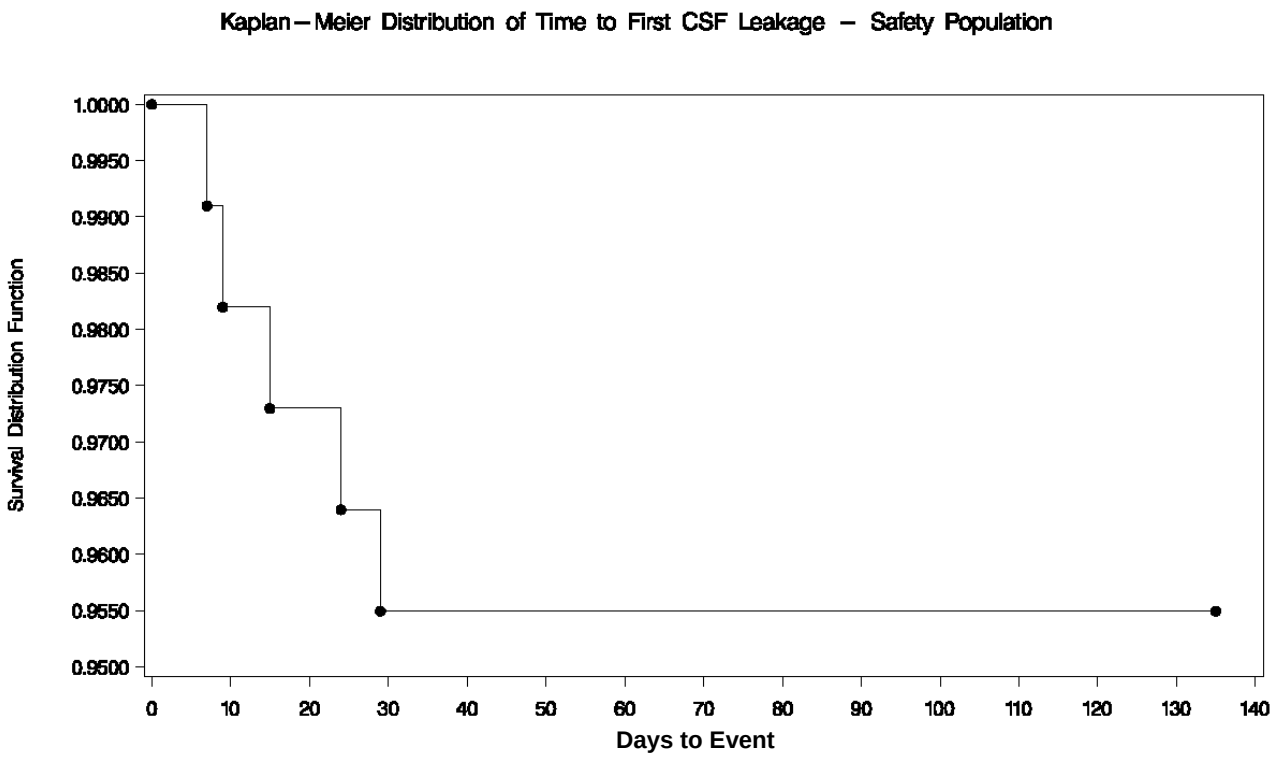
Safety was assessed based on evaluation of wound healing, the occurrence of post-operative CSF leaks, the nature and severity of other adverse events, and adverse device-related adverse events diagnosed by physical examination, protocol-specified diagnostic laboratory tests, neurological assessments (including pain and modified Rankin Scale) and CT imaging assessment performed by independent neuroradiologists for evaluation of extradural collections and unexpected findings.

There were no unanticipated adverse device effects. There were two patient deaths (out-of-hospital). In both cases, the deaths were attributed to the patients' prior condition or neurosurgical procedure.

The incidence and nature of adverse events observed in this patient population are consistent with the type and complexity of the surgery performed and the co-morbid state of the treated patients. Thirty-two patients (29%) experienced a total of 54 serious adverse events (SAE). Relationship to the study-device was "not related" for 78% of SAE reports and 22% were "unable to determine" including 6 patients with events of deep surgical site infections, 3 patients with cerebrospinal fluid (CSF) leaks and 1 patient with headaches that did not respond to standard therapy which preceded a CSF leak.

The Kaplan-Meier estimate for freedom from CSF Leakage at 135 days following surgery is 95.5%, which corresponds to a leak rate of 4.5% [95% C.I: 0.65% to 8.4%]. Time to first endpoint CSF leakage ranged from 7 to 29 days.

Figure 1. Kaplan-Meier Analysis: Freedom from CSF Leakage



The incidence of post-operative CSF leaks compares quite favorably to that reported in the literature (generally 10.6%).

Deep surgical site infections occurred in 7.2% of patients (8 patients out of 111; with a total of 9 events documented due to a worsening of 1 event). The incidence of post-operative surgical site infections can be compared with that of commercially available duroplasty materials with reported infection rates up to 6.1%. Patients who smoke or had a history of smoking within the previous 10 years, were five times more likely to experience an infection. DuraSeal Sealant volume was not an independent predictor of infection. For all patients the wounds were noted to be well healed by three months.

There was no untoward effect on hepatic or renal function associated with product use and absorption. Additionally, there were no unexpected findings based on CT imaging assessment by independent neuroradiologists. Based on CT imaging, the average reduction in extradural space at the DuraSeal Sealant application site is 74% at 3 months, suggesting DuraSeal absorption.

European Pilot Trial

A prospective, single center, non-randomized clinical investigation to evaluate the safety and performance of the DuraSeal Dural Sealant System in patients scheduled for elective cranial or spinal surgery was performed in the Netherlands.

A total of 47 patients were treated with the DuraSeal Dural Sealant System; 45 (95.7%) cranial and 2 (4.3%) spinal intra-dural procedures.

The primary endpoint of this study was a reduction in the incidence of intra-operative cerebrospinal fluid (CSF) leakage following dural sealant application defined as:

> *Success* = No CSF leakage from dural repair intra-operatively during Valsalva maneuver (20 cm H_20),
> *Failure* = CSF leakage that results after Dural Sealant application(s) during Valsalva maneuver (20 cm H_20).

None of the 47 patients treated with the DuraSeal System demonstrated a CSF leak during the post application Valsalva maneuver, thus demonstrating a 100% success rate in holding a watertight seal. The incidence of clinically diagnosed post-op CSF leaks was 4.7%, the incidence of pseudomeningocele was 2.3%.

The primary safety endpoint was defined as procedure-related complications and adverse events. There were a total of 51 adverse events reported in 28 patients; there were 14 serious adverse events in 11 patients or an overall incidence of 29.8% in the study. None of the reported adverse events were deemed related to the DuraSeal System.

CONCLUSIONS DRAWN FROM STUDIES

Results from preclinical studies indicate that the DuraSeal Dural Sealant System meets or exceeds safety and performance specifications. Multi-center clinical data have demonstrated that DuraSeal Dural Sealant is safe and effective when used as an adjunct to sutured dural repair during cranial surgery to provide watertight closure. Results from the preclinical and clinical evaluations provide valid scientific evidence and reasonable assurance that the device is safe and effective when used in accordance with the labeling.