SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Surgical Sealant, Polymerizing

Device Trade Name: DuraSeal Spine Sealant System

Applicant's Name and Address: Covidien
101A First Avenue
Waltham, MA 02451

Date of Panel Recommendation: May 14, 2009

Premarket Approval Application (PMA) Number: P080013

Date of FDA Notice of Approval: September 4, 2009

Expedited: Not applicable

II. INDICATIONS FOR USE

The DuraSeal Spine Sealant System is indicated for use as an adjunct to sutured dural repair during spinal surgery to provide watertight closure.

III. CONTRAINDICATIONS

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

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the DuraSeal™ Dural Sealant System labeling.

V. DEVICE DESCRIPTION

The DuraSeal Spine Sealant System consists of components for preparation of a synthetic absorbable sealant, and applicators for delivery of the sealant to the target site. The DuraSeal Spine Sealant produced by the DuraSeal Spine Sealant System is composed of two solutions, a PEG ester solution and a Trilysine amine solution (which are referred to as the "blue" and "clear" precursors, respectively). When mixed together, the precursors rapidly polymerize in-situ to form the hydrogel sealant. The mixing of the precursors is accomplished in the delivery system as the materials exit the tip of the

delivery system. The delivery system allows a conformal coating that adheres to the tissue surfaces. The mixing provided by the delivery system also ensures a complete reaction of the precursors. The polymerization requires no external energy requirements, such as light or heat, and takes place by a nucleophilic substitution reaction. The PEG component contains hydrolyzable ester bonds which enable the hydrogel to be degraded through hydrolysis after application. FD&C Blue no. I dye provides the color of the blue solution and enables the user to discern the thickness of the hydrogel layer and the area of hydrogel application. The gel swells, volume metrically, no more than 200%. For a 2 mm thick hydrogel that isotropically swells 200%, the maximum linear dimensional change in any direction is <1 mm. There is very little or no heat evolution during the polymerization reaction.

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 material is absorbed in approximately 4 to 8 weeks and the absorbed hydrogel components are excreted from the body. The DuraSeal Spine Sealant can be used for up to one hour following reconstitution.

The DuraSeal Spine Sealant System is provided in two configurations. The 2 mL configuration consists of one 2 mL polymer kit and one MicroMyst™ Applicator (the MicroMyst Applicator requires the use of a compressed air source, such as the Confluent Surgical Flow Regulator or the Confluent Surgical Air Pump).The 5 Ml configuration, consists of one 5 mL polymer kit, which includes the Dual Liquid Applicator (consisting of the Y-Applicator and three (3) Spray Tips).

VI. 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 application of absorbable gelatin or collagen sponge, autologous muscle, temporalis fascia, fascia lata, ligamentum nuchae or fat grafts.

VII. MARKETING HISTORY

The DuraSeal Spine Sealant System contains the same hydrogel sealant as used in the currently marketed DuraSeal Dural Sealant System (PMA P040034). The chemical composition of the hydrogel sealant used in both products is identical in formulation.

The DuraSeal Dural Sealant System has been marketed outside the United States since 2003 as an adjunct to standard methods of dural repair to provide watertight closure in cranial and spine procedures. The DuraSeal Spine Sealant System, 2 mL configuration, has been marketed outside of the United States since 2005 as an adjunct to standard

methods of dural repair, such as sutures, to provide watertight closure during spine procedures.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

In the pivotal clinical study, 102 patients were treated with the DuraSeal Spine Sealant System and 56 patients were treated using Standard of Care (Control) methods. All Adverse Events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and are presented based on System Organ Class in Table 1: Adverse Events by System Organ Class.

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 patient deaths.

Table 1 Adverse Events by System Organ Class

System Organ Class	DuraSeal Spine Sealant (N=102) n (%)	Control (N=56) n (%)
Any Adverse Event	95 (93.1)	51 (91.1)
Blood And Lymphatic System Disorders	10 (9.8)	4 (7.1)
Cardiac Disorders	10 (9.8)	2 (3.6)
Eye Disorders	6 (5.9)	1 (1.8)
Gastrointestinal Disorders	21 (20.6)	9 (16.1)
General Disorders And Administration Site Conditions	33 (32.4)	18 (32.1)
Immune System Disorders	1 (1.0)	0 (0.0)
Infections And Infestations	19 (18.6)	9 (16.1)
Injury, Poisoning And Procedural Complications*	44 (43.1)	7 (12.5)
Investigations	50 (49.0)	23 (41.1)
Metabolism And Nutrition Disorders	10 (9.8)	3 (5.4)
Musculoskeletal And Connective Tissue Disorders	24 (23.5)	15 (26.8)
Neoplasms Benign, Malignant And Unspecified (Including Cysts And Polyps)	4 (3.9)	0 (0.0)
Nervous System Disorders*	48 (47.1)	21(37.5)
Psychiatric Disorders	4 (3.9)	3 (5.4)
Renal And Urinary Disorders*	20 (19.6)	4 (7.1)

Reproductive System And Breast Disorders	1 (1.0)	1(1.8)
Respiratory, Thoracic And Mediastinal Disorders	15 (14.7)	4 (7.1)
Skin And Subcutaneous Tissue Disorders	9 (8.8)	3 (5.4)
Vascular Disorders	10 (9.8)	6 (10.7)

* See *Analysis of Adverse Events* Section (Pgs.20-25) for details.

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. Potential, but not observed, risks and adverse events that could occur from the use of the DuraSeal Spine Sealant System include, but are not limited to, renal compromise, inflammatory reaction, neurological compromise, allergic reaction and/or delayed healing.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Biocompatibility

Biocompatibility testing was performed on 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 evaluated the delivery systems (i.e., Dual Liquid Applicator and MicroMyst Applicator) for biocompatibility.

Biocompatibility testing (Table 2) of the formed 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 hydrogel as a tissue/bone contacting implant of permanent contact duration.

Table 2 Summary of DuraSeal Spine 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

Test Reference	Method Reference	Results
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*	Non-pyrogenic
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
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

Test Reference	Method Reference	Results
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*	Non-hemolytic
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.

***In Vitro* Product Testing**

A series of *in vitro* tests (table 3) were performed on the components and materials of the DuraSeal Spine Sealant System (final, sterilized devices).

Table 3 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 mixed (gel time), and 1 hour after reconstitution of the blue precursor (pot life).	Upon mixing precursors, a gel is formed in ≤ 3.5 seconds.
Swelling	Evaluates the percent weight gain resulting from a 24-hour immersion of the hydrogel in 37°C phosphate buffered saline (PBS).	In vitro swelling is ≤ 200%.

Design Characteristic	Test Description	Results
In vitro absorption – disappearance	Hydrogel time of dissolution when placed in Phosphate Buffered Saline (PBS) at 60.4 °C.	DuraSeal Spine Sealant hydrogel is visibly dissolved in 1.3 to 3.6 days after immersion into the phosphate buffered solution, pH of 7.4 at 60.4°C.
Buffer pH	Trilysine/Borate buffer pH is a determinant of gel time. Borate buffer pH is measured for the batch solution in production. Borate buffer pH in the individual syringes is monitored as a confirmation of the manufacturing controls.	The trilysine/borate buffer pH shall be between 10.01 and 10.37.
PEG Ester Vial Oxygen Content	Measures the oxygen content in the PEG ester powder vial. The PEG backbone is susceptible to oxidative chain scission, which can decrease the cross-link density of the material resulting in altered performance characteristics (i.e., increased gel times, increased swelling and shorter disappearance times).	The PEG Ester Vial Oxygen content shall be ≤ 1 %.
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 fluid lumens shall not leak or fail when pressurized to 68 psi for a minimum of 4 seconds.
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 1-4cm from target tissue.

Sterilization

E-beam irradiation sterilization to a Sterility Assurance Level (SAL) of 1 x 10^{-6}, validated in accordance with "AAMI/ANSI/ISO11137:1995(E), *Sterilization of health care products –Requirements for validation and routine control – Radiation Sterilization*",

"EN 552:1994, *Sterilization of medical devices - Validation and routine control of sterilization by irradiation*", "AAMI TIR No. 27:2001, *Sterilization of healthcare products – Radiation sterilization – Substantiation of 25 kGy as a sterilization dose, Method VD_{max}*", and "ANSI/AAMI/ISO 11737-1:1995, *Sterilization of medical devices – Microbiological methods – Part 1: Estimation of the population of microorganisms on products*".

Shelf Life

An 18-month shelf life was established based on both real-time and accelerated aging studies. The devices were tested for the following attributes following real-time and accelerated aging:

- Visual assessment
- Hydrogel performance
- Packaging assessment

B. Animal Studies

A series of animal studies were conducted to evaluate the *in vivo* performance and safety of the DuraSeal Spine Sealant System. Table 4 provides a summary of the tests performed and the relevant findings.

Table 4 Summary of Animal Studies

Test Performed	# Animals/ Study Duration	Summary/Relevant Findings
Dural Sealing in a Canine Cranial Model	13 test (hydrogel) and 13 control/56 days	Study performed to demonstrate both safety and effectiveness of the hydrogel as a dural sealant. Study endpoints included sealing capability of Cerebrospinal fluid (CSF) leaks after treatment with the hydrogel ("test") when compared with control ("no treatment") following challenge with a Valsalva maneuver, and confirmation of normal healing (tolerance) following application of the hydrogel. 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 treated and control arms were terminated. Marked peridural adhesions were encountered in 3/3 control dogs at 7 days, and 1/3 control dogs at 56 days; no dural adhesions were observed in the treated arm. Valsalva at 1, 4, 7 and 56 days showed mean leakage pressures of, respectively: 5, 5, 7 and 13 cm H_20 in controls and 53, 37, 42 and 48 cm H_20 in treated animals. Histopathology of controls showed thick dural fibroplasias with little or no injury to the underlying brain; in hydrogel treated animals, both dura-

Test Performed	# Animals/ Study Duration	Summary/Relevant Findings
		arachnoid complex and brain displayed minimal changes. Evidence of residual implant hydrogel material was less evident at the 7 day re-explorations, and had completely disappeared by 56 days. The results obtained from this controlled Study suggest that the hydrogel is effective as a tissue Sealant to achieve optimal dural closure and repair, and that the hydrogel material is well tolerated.
Hydrogel Appearance under MR and CT Imaging	2 test (hydrogel)/14 weeks	An evaluation was undertaken to determine the Magnetic Resonance (MR) and Computed Tomography (CT) imaging characteristics of the hydrogel following implantation. Additionally, histological evaluation was performed to evaluate for potential local toxicity and/or space filling defect. Following a craniotomy in two canines, the hydrogel 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. The hydrogel 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 hydrogel. Histological examination found an unremarkable response with no neurotoxicity, or space-filling defect.
Implantation of Hydrogel in Rat Brain Parenchyma	8 test (hydrogel) and 8 control/42 days	The hydrogel was evaluated for the potential to cause local irritation or toxicity at the implant site. Micro forceps were used to implant pieces of the hydrogel 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 arm were euthanized. No neurologic deficits were noted and no adverse reactions were observed for any of the test sites at explant.
Neurotoxicity Study in the Rat Following Injection into the Brain	13 test (hydrogel) and 13 control/2 weeks	The potential neurotoxicity of the hydrogel 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

Test Performed	# Animals/ Study Duration	Summary/Relevant Findings
		each cannulation type and treatment arm 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.
Evaluation of Hydrogel Persistence Following Subcutaneous Implantation in the Rat	21 test (hydrogel) and 21 control/14 weeks	Results demonstrate that the hydrogel persists essentially in its initial form for 2 weeks, becomes noticeably softer at 4 weeks and is predominantly degraded by 6 weeks. Results of this Study document that in vivo absorption of the hydrogel is complete within 8 weeks of implant. The hydrogel to be used in the spine is identical in chemical composition to the hydrogel evaluated in this Study. Study performed to evaluate the *in vivo* persistence and degradation of the hydrogel over a period of 14 weeks following subcutaneous implantation in the rat.
Study for Effects on Embryo-Fetal Development in Rats Following Intraperitoneal Administration	25 test (hydrogel) and 25 control/2 weeks	Study performed to determine the developmental toxicity, including the teratogenic potential of the hydrogel 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 the Sealant to a control substance. Based on the results of this Study, the No Observable Effect Level (NOEL) for maternal and developmental effects is >0.1 mL (0.3909 mL/kg) of hydrogel, which represents almost 5.5 times the anticipated exposure under normal conditions of use. Under the conditions of this Study, the hydrogel was found to be non-teratogenic in rats.
Canine Lumbar Laminectomy Study	13 animals, two surgical sites per animal: treatment (hydrogel) or surgical control (no treatment)/12 - 14 weeks	Study was performed in a canine lumbar laminectomy model. Following laminectomies at L3 and L5, the two surgical sites were randomized to either hydrogel treatment or control. All animals were terminated at 12-14 weeks post-operatively. Animals were observed to qualitatively assess general health, normal behavior, and for possible neurological abnormalities. Specific neurological examinations were performed on the animals in this Study. The exam was designed to test reflexes moderated in the area of the surgery and pathways, which ascend or descend through the surgical area. Scar tissue formation was evaluated using gross dissection and

Test Performed	# Animals/ Study Duration	Summary/Relevant Findings
		histopathology. None of the animals tested exhibited any evidence of neurological lesions. The general health of the animals remained excellent throughout the Study. Other than the one that had to be euthanized, no animals exhibited neurological, behavioral or health problems. The extraspinal tissue had healed normally, and both the treated and control sites exhibited the same amount of bone regrowth. Gross pathological and histopathological examinations showed that the hydrogel decreased the severity and incidence of periosteal-dural adhesions. The extraspinal tissue had healed normally, and both the treated and control sites exhibited the same amount of bone regrowth. Gross pathological and histopathological examinations showed that the hydrogel decreased the severity and incidence of periosteal-dural adhesions.
Cauda Equina Study in the Canine	9 animals each assigned to treatment arm (hydrogel) or surgical control (no treatment)/8 weeks.	Study was performed in a canine cauda equina discectomy model, and the hydrogel was applied to the lumbar region following spinal surgery using a fine air-assisted sprayer (i.e., MicroMyst Applicator). Animals were observed daily for general health with emphasis on neurological deficits and pain and neurological examinations were conducted at specific intervals up to 8 weeks. Wound healing, tissue response, scar formation and nerve root mobility were evaluated using gross dissection and histopathology. Test animals were healthy over the course of the Study with no neurologic sequelae or adverse effects associated with the test article. Sub-gross findings showed increased nerve root mobility in treated animals (reduced scar formation), while histological specimens indicated less scar impingement into the spinal canal in hydrogel treated animals.

C. Additional Studies

Dye Toxicology Evaluations

The DuraSeal Spine Sealant contains FD&C Blue #1 dye for visualization of the hydrogel during application. The dye is a certified color listed in 21 CFR 82 and it has been approved for use in foods (21 CFR 74.101), drugs (21 CFR 74.1101) and cosmetics (21CFR 2101). FD&C Blue #1 is water soluble and has been evaluated in life-exposure animal studies that determined an acceptable daily intake (ADI) for the dye of 12 mg/kg/day. Calculations comparing the amount of dye absorbed by ingestion, and the amount of dye a patient will be exposed to in one application of DuraSeal Spine Sealant, indicate that the absorbed amount of ingested dye would be much greater. In vitro and in vivo determinations found low microgram/mL concentrations after 9 hours of elution

from polymerized gel in a saline bath or undetectable amounts (low microgram detection sensitivity) of the dye at 7-8 days, post-implantation in a dog model. The dye was determined to not be present in the body for a significant amount of time.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of sutured dural repair using the Duraseal Spinal Sealant as an adjunct to sutures, to provide watertight closure, in the US under IDE G050063. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A) Study Design

US Pivotal Trial
Subjects were treated between September 1, 2005 and February 6, 2008. The database for this PMA reflected data collected through February 6, 2008 and included 158 subjects. There were 24 investigational sites.

The study was a prospective, multi-center, randomized, two-arm, single blind clinical investigation was conducted to evaluate the safety and effectiveness of the DuraSeal Spine Sealant System, when used as an adjunct to sutured dural repair, as compared to Standard of Care methods (Control) for producing a watertight dural closure in subjects undergoing an intentional durotomy during spinal surgery. The Study involved 24 investigational sites within the United States. A total of 158 subjects were enrolled, including 102 subjects treated with the DuraSeal Spine Sealant, and 56 subjects treated using Standard of Care (Control) methods.

The control group was 56 subjects treated using Standard of Care (Control) methods.

1. **Clinical Inclusion and Exclusion Criteria**
Enrollment in the DuraSeal Spine Pivotal Study (DRS 05-001) was limited to patients who met the following inclusion criteria:

Pre-Operative Inclusion Criteria
- 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

Pre-Operative Exclusion Criteria
Patients were not permitted to enroll in the DuraSeal Spine Pivotal Study (DRS 05-001) study if they met any of the following exclusion criteria:

- 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 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 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

Intra-Operative Inclusion Criteria

- Surgical wound classification Class I/Clean (per CDC criteria)
- 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

Intra-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
- Incidental finding of any of the Pre-operative Exclusion Criteria

2. **Treatment and Follow-Up Procedures**

Prior to initiation of enrollment, all Study surgeons were trained on the proper use of the DuraSeal Spine Sealant System. Patients who were scheduled for an elective spinal procedure that required a dural incision and who met pre-operative Study eligibility criteria were invited to participate in the Study. Informed consent and a baseline evaluation including laboratory testing were performed prior to surgery.

The investigator performed the spinal procedure and sutured dural repair according to the standard procedures and practices at his/her institution. Autologous duraplasty materials (i.e., fascia, fat, pericranium, or muscle) were used as necessary to augment dural closure.

Following primary dural closure, the subject was evaluated to confirm intra-operative eligibility. The dural repair was evaluated for the presence or absence of watertight closure with a baseline Valsalva maneuver at 20-25 cm H_20 for 5-10 seconds. If there was a spontaneous expression of CSF, no Valsalva maneuver was required. The type (e.g, overt versus seepage of CSF around the suture points) and the nature of the non-watertight closure (i.e., spontaneous versus upon Valsalva) was recorded.

If non-watertight closure was present, the subject was randomized to either DuraSeal Spine Sealant or Control. Randomization was based on an approximately 2:1 (Sealant: Control) ratio. Randomization was considered the point of enrollment; therefore, subjects that did not meet the intra-operative eligibility criteria were withdrawn from the Study without additional follow-up.

Following treatment of the dural incision with either the DuraSeal Spine Sealant or chosen Standard of Care methods, subjects were assessed for the primary efficacy endpoint, defined as a watertight closure of the dural repair intra-operatively, confirmed by Valsalva maneuver at 20-25 cm H_20 for 5-10 seconds.

Following surgery, subjects were seen at the following time points: Discharge (within 7 days post-operative, but prior to hospital discharge), 30 Day post-operative visit (-7 days/+ 14 days) and 90 Day post-operative visit (± 14 days). The follow-up visits included a physical exam, complete neurological exam, CSF leak evaluation, surgical site infection assessment and wound healing evaluations, laboratory testing, pain Visual Analog Scales (VAS) and quality of life self-assessments (SF-36). Additionally, any reported adverse events were documented for each of the assessment intervals.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. **<u>Clinical Endpoints</u>**

Safety and Effectiveness Parameters:

The primary effectiveness endpoint for the Study was the percent success in obtaining a watertight closure following assigned treatment (DuraSeal Spine Sealant or Control). Success is defined as a watertight closure of the dural repair intra-operatively after treatment, confirmed by Valsalva maneuver at 20-25 cm H_2O for 5-10 seconds.

Safety endpoints include the following:
Presence or absence of CSF leaks within 90 days post-operatively as determined from clinical diagnosis by one of the following methods:

- CSF leak or pseudomeningocele related surgical intervention (i.e., breaking skin) within 90 days post-procedure; or
- CSF leak confirmation by diagnostic testing within 90 days post-procedure; or
- CSF leak confirmation by clinical evaluation within 90 days post-procedure
- Presence or absence of surgical site infection within 90 days post-procedure determined from clinical diagnosis in accordance with the Center for Disease Control definitions of surgical site infections (Superficial Surgical Site Infection, Deep Surgical Site Infection, Organ/Space Surgical Site Infection).

- Additional safety evaluations include the incidence of adverse events, protocol-specified diagnostic laboratory tests, neurological assessments (including cranial nerve, neurological, motor, sensory, reflex, gait, and symptoms of nerve root compression), and wound healing assessment.

A. Study Population Demographics and Baseline Parameters

The demographics of the study population are *typical* for a durotomy study performed in the US.

The Study involved 24 investigational sites within the United States. A total of 158 subjects were enrolled in the Study. Of those, 102 subjects were treated with the DuraSeal Spine Sealant System and 56 subjects were treated using Control methods. Of the 158 subjects, 153 subjects (96%) completed the 90-day follow-up visit. Subject demographics are provided in Table 5 Subject Demographics.

Table 5 Subject Demographics

CHARACTERISTICS	DURASEAL SPINAL SEALANT (N=102) N (%)	CONTROL (N=56) N (%)
Age (years)		
Mean (SD)	47.7 (13.68)	42.3 (14.57)
Range (min, max)	(18.7 ,74.5)	(19.5 ,74.2)
Gender, n(%)		
Female	54 (52.9)	30 (53.6)

Male	48(47.1)	26 (46.4)
Height (cm)		
Mean (SD)	169.9 (11.74)	169.8 (12.52)
Range (min, max)	(132.1 ,188.0)	(132.1 ,193.0)
Weight (Kg)		
Mean (SD)	80.8 (20.62)	83.9 (24.31)
Range (min, max)	(45.7 ,147.4)	(36.0 ,180.0)
BMI (Kg/m^2)		
Mean (SD)	27.8 (6.09)	29.0 (7.74)
Range (min, max)	(17.9 ,46.2)	(16.0 ,64.0)
Smoking Status, n(%)		
Never	62 (60.8)	27 (48.2)
History	21 (20.6)	20 (35.7)
Current	19 (18.6)	9 (16.1)
ASA Score, n(%)		
I	13 (12.7)	4 (7.1)
II	66 (64.7)	40 (71.4)
III	22 (21.6)	12 (21.4)
IV	1 (1.0)	0 (0)
Type of Procedure	DuraSeal Spinal Sealant (N=102) n (%)	Control (N=56) n (%)
A-V malformation	0 (0.0)	1 (1.8)
Chiari	22 (21.6)	18 (32.1)
Cyst	8 (7.8)	0 (0.0)
Syringomyelia	4 (3.9)	1 (1.8)
Syringomyelia with arachnoid cyst	1 (1.0)	0 (0.0)
Tethered cord	3 (2.9)	1 (1.8)
Tumor removal	64 (62.7)	35 (62.5)

The study procedures fell across all regions in the spine from cervical to sacral in both the Spinal Sealant arm and the Control arm, refer to Table 6 Location of Procedure.

Table 6 Location of Procedure

Location of Procedure (%)	DuraSeal Spinal Sealant (N=102)	Control (N=56)
Cervical	47	32
Thoracic	39	15
Lumbar	25	15
Sacral	9	1

B. Safety and Effectiveness Results

The safety population includes all subjects treated in the Study.

Safety of the DuraSeal Spinal Sealant has been assessed per protocol defined criteria. Specifically, the evaluation of the presence of post-operative CSF leaks within 90 days post-procedure, presence of surgical site infection within 90 days post-procedure (in accordance with the Centers for Disease Control definitions of surgical site infection. Additionally, subjects underwent safety assessments via evaluation of neurological status, laboratory testing, wound healing and review of spontaneously reported adverse events.

All adverse events were reviewed by an independent unblinded Clinical Events Committee (CEC). The CEC was comprised of three, board certified neurosurgeons. The CEC was provided a summary of the subject's medical history/current condition, applicable procedural information, and summaries of the specific adverse events. When appropriate, de-identified source documentation (e.g., history, operative report, post-operative progress notes and summaries of diagnostic tests performed) were provided to aid the CEC's review. The CEC's review served as a formal independent adjudication and validation of events in the Study, as well as a mechanism to continuously monitor subject safety during the course of the Study. For the majority of the reported events, the CEC concurred with the treating investigator's assessment of an event. However, for certain minor events it was the CEC's determination that the reported events did not meet the criteria of an adverse event, and deemed such specific reports as "non-events". Conservatively, safety data are presented based on the treating investigator's reporting. All reported events have thus been summarized.

Verbatim adverse event terms as recorded by the investigative site staff were coded using the MedDRA medical dictionary (version 9.1) and data have been presented by System Organ Classes (SOCs) and Preferred Term (PT). The coding of adverse events was performed by an independent contractor (Boston Biomedical Associates, Northboro, MA)

and was reviewed by a safety specialist (a registered nurse). Furthermore, the coded data were verified by a member of the CEC to further assure that the data was accurately presented.

AEs are summarized, for each treatment arm, by SOC/PT and severity. The first part of the following safety summary focuses on the incidence of post-operative CSF leaks and surgical site infections, as defined in the protocol. Adverse event data is presented in total with additional discussion and attention focused on those events meeting the protocol definition for "serious". Specific discussions pertinent to other safety information such as results of laboratory diagnostic tests, neurological assessments and wound healing are also presented.

Post-operative CSF leaks

One of the pre-specified safety endpoints is the incidence of CSF leaks within 90 days of the index procedure. Subjects were closely monitored for evidence of CSF leaks as determined from clinical diagnosis by **ANY** one of the following methods:

- CSF leak or pseudomeningocele related surgical intervention (i.e., breaking skin) within 90 days post-procedure; or
- CSF leak confirmation by diagnostic testing within 90 days post-procedure; or
- CSF leak confirmation by clinical evaluation within 90 days post-procedure

Post-operative protocol defined CSF leaks diagnosed using the above definition occurred in 7.8% and 5.4% of subjects in the DuraSeal Spinal Sealant and Control arms respectively, Table 7 Incidence of Protocol Defined Post-Operative CSF Leaks. This difference is not statistically significant, p=0.748, two sided Fisher test.

Table 7 Incidence of Protocol Defined Post-Operative CSF Leaks

Category	Statistic	DuraSeal Spinal Sealant (N=102)	Control (N=56)	Difference (%)
Presence of endpoint CSF leak within 90 days post-procedure	n (%)	8 (7.8)	3 (5.4)	2.5
CSF Fistula	n	3 (2.9)	0	2.9
Pseudomeningocele	n	5 (4.9)	3 (5.4)	0.5

All available subject assessment data were utilized in performing a Kaplan-Meier analysis to estimate the proportion of subjects experiencing protocol defined post-operative CSF leaks by 90 days. Subjects not evaluable at 90 days are counted in the Kaplan-Meier analysis through the point of the last evaluation, Table 8 Endpoint CSF Leakage (Safety Population).

Table 8 Endpoint CSF Leakage (Safety Population)

Endpoint	Statistic	DuraSeal Spinal Sealant (N=102)	Control (N=56)	Difference (%)
Presence of endpoint CSF leak within 90 days post-procedure	n (%)	8(7.8)	3(5.4)	2.5
	p-value (1)	0.748		
Cumulative proportion of CSF leak within 90-days post-procedure	n (%)	8(8.4)	3(5.6)	2.8
	95% CI	(4.3, 16.3)	(1.8, 16.4)	(-5.6, 11.2)
	p-value (2)	0.570		

In this analysis, the estimated proportion of subjects experiencing a protocol defined post-operative CSF leak in the DuraSeal Spinal Sealant and Control arms, respectively, are 8.4% [95% C.I: 4.3% to 16.3%] and 5.6% [95% C.I: 1.8% to 16.4%]. This difference is not statistically significant (p =0.570, log rank test). The time to first protocol defined post-operative CSF leak ranged from 3 to 42 days in the DuraSeal Spinal Sealant arm and from 27 to 59 days in the Control arm.

Surgical Site Infections

Surgical Site Infections (SSIs) were diagnosed and classified in accordance with the Centers for Disease Control (CDC) criteria for evaluation and diagnosis of nosocomial surgical site infections and were classified as one of the following:

- **Superficial Surgical Site Infection**: Infection occurs within 30 days after the operation and infection involves only skin or subcutaneous tissue of the incision

- ***Deep Surgical Site Infection:*** Infection occurs within 1 year if implant is in place and the infection appears to be related to the operation *and* infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision

- ***Organ/Space Surgical Site Infection***: Infection occurs within 1 year if implant is in place and the infection appears to be related to the operation *and* infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation. Note per the CDC guidance, organ/space surgical site infectio2ns that occur concomitantly with a deep surgical site infection, is to be categorized as a deep surgical site infection.

Post-operative SSIs as diagnosed using the above definitions occurred in 6.9% and 7.1% of subjects in the DuraSeal Spinal Sealant and Control arms, respectively. This difference was

not statistically significant, p=1.00, two sided Fisher test, Table 9 Incidence of Surgical Site Infections.

Table 9 Incidence of Surgical Site Infections

Category	DuraSeal Spinal Sealant (N=102) n (%)	Control (N=56) n (%)	Difference (%)	95% CI for Difference
Presence of SSI within 90 days post-procedure	7 (6.9)	4 (7.1)	-0.2	-8.6, 8.1
Deep Surgical Site Infection	5 (4.9)	1(1.7)	-3.2	-2.3, 8.6
Superficial Surgical Site Infection	2(2.0)	3(5.4)	3.4	-9.2, 4.3

Subjects not evaluable at 90 days are counted in the Kaplan-Meier analysis through the point of the last evaluation and therefore, this analysis takes into account that not all subjects completed the trial. In this analysis, the estimated proportions of subjects experiencing a SSI in the DuraSeal Spinal Sealant and Control arms, respectively, are 6.9% [95% C.I: 3.4% to 14.0%] and 7.4% [95% C.I: 2.8% to 18.5%] (p =0.902, log rank test). The time to diagnosis of the SSI ranged from 9 to 25 days in the DuraSeal Spinal Sealant arm and from 10 to 20 days in the Control arm.

Six subjects experienced deep SSI, five of which occurred within the DuraSeal Spinal Sealant arm. Of those five subjects, 4 had undergone removal of a spinal tumor or cyst and one subject underwent a procedure for Syringomeylia associated with a Chiari Malformation. All five subjects were cultured and found positive for various organisms. Two cultures tested positive for Methicillin resistant Staphylococcus aureus (MRSA) which is a finding consistent with hospital acquired infections. All but one event (DuraSeal Spinal Sealant Subject, 14-006) resolved without sequelae by the 90 post-operative visit. Subject 14-006, who was treated for a deep surgical site infection, had not completely recovered by the 90 day follow-up but she was noted to have improved at the last Study visit.

All the events were deemed not related to the device and in fact in the majority of cases the CEC determined that infections were related to the subjects' procedures. For the one subject within the Control arm that experienced a deep SSI, the infection was concomitant with a CSF leak and the subject developed bacterial meningitis (Subject 06-013).

Adverse effects that occurred in the PMA clinical study:

Adverse Events, Serious Adverse Events and Device Related Adverse Events
Serious adverse events (SAEs) and device-related adverse events were also examined separately.

Adverse Event Overview

Table 10 Summary of Adverse Events (AEs) and Serious Adverse Events (SAEs) provides an overview of the incidence of adverse events by category. Overall, 93.1% of subjects within the DuraSeal Spinal Sealant arm and 91.1% within the Control arm experienced at least one AE, and 29.4 % and 17.9% of subjects within the DuraSeal Spinal Sealant and Control arms, respectively, experienced at least one SAE. There were no unanticipated adverse device effects noted for both treatment arm and only one subject within the DuraSeal Spinal Sealant arm (1.0%) was noted to have a device-related event as determined by the investigator.

Table 10 Summary of Adverse Events (AEs) and Serious Adverse Events (SAEs)

Category	DuraSeal Spinal Sealant (N=102) n (%)	Control (N=56) n (%)
Number of Subjects (%) With At Least One AE	95 (93.1)	51 (91.1)
Number of Subjects (%) With At Least One SAE	30 (29.4)	10 (17.9)

Event severity was classified by the investigator applying the following definitions:

- Mild: Awareness of signs or symptoms, but easily tolerated; minor irritant requiring medication or a medical evaluation; signs and symptoms are transient, resolved during the procedure.
- Moderate: Discomfort/deficit severe enough to cause interference with usual activities; persists after procedure or requires treatment, but does not extend hospitalization or intensive care for the subject.
- Severe: Fatal or life-threatening, results in persistent or significant disability, requires intervention to prevent permanent impairment/damage, or results in congenital anomaly, cancer, readmission, or prolongation of hospitalization.

As shown in Table 11 Summary of Severity of Adverse Events, within both treatment arms, the majority of AEs were mild to moderate in severity. With the exception of one event, subject 03-001 who experienced a pseudomeningocele that required a surgical repair and was deemed to be related to the DuraSeal Spinal Sealant per the investigator. The CEC adjudicated the event not related to the DuraSeal Spinal Sealant.

Table 11 Summary of Severity of Adverse Events

Treatment arm	Mild	Moderate	Severe
DuraSeal Spinal Sealant (N=425), n%	269(63.3)	118(27.8)	38(8.9)
Control (N=165), n%	108(65.5)	43(26.1)	14(8.5)

Analysis of Adverse Events

As noted previously, 93.1% of subjects within the DuraSeal Spinal Sealant arm and 91.1% within the Control arm experienced at least one AE. Adverse events most often occurred in the "Nervous System Disorders", "Musculoskeletal, Connective Tissue and Bone Disorders", "Infections and Infestations", "Metabolism and Nutrition Disorders", and "Gastrointestinal Disorders" categories.

Table 12 Adverse Events by System Organ Class (Safety Population) presents the incidence of adverse events within each System Organ Class.

Table 12 Adverse Events by System Organ Class (Safety Population)

System Organ Class	DuraSeal Spinal Sealant (N=102) (%)	Control (N=56) (%)	95% CI of Difference
Blood And Lymphatic System Disorders	10 (9.8)	4 (7.1)	(-6.2, 11.5)
Cardiac Disorders	10 (9.8)	2 (3.6)	(-1.3, 13.8)
Eye Disorders	6 (5.9)	1 (1.8)	(-1.6, 9.8)
Gastrointestinal Disorders	21 (20.6)	9 (16.1)	(-7.9, 16.9)
General Disorders And Administration Site Conditions	33 (32.4)	18 (32.1)	(-15.0, 15.4)
Immune System Disorders	1 (1.0)	0 (0.0)	(-0.9, 2.9)
Infections And Infestations	19 (18.6)	9 (16.1)	(-9.7, 14.8)
Injury, Poisoning And Procedural Complications	44 (43.1)	7 (12.5)	(17.7, 43.6)
Investigations	50 (49.0)	23 (41.1)	(-8.2, 24.1)
Metabolism And Nutrition Disorders	10 (9.8)	3 (5.4)	(-3.8, 12.7)
Musculoskeletal And Connective Tissue Disorders	24 (23.5)	15 (26.8)	(-17.5, 11.0)

Neoplasms Benign, Malignant And Unspecified (Including Cysts And Polyps)	4 (3.9)	0 (0.0)	(0.2, 7.7)
Nervous System Disorders	48 (47.1)	21 (37.5)	(-6.4, 25.5)
Psychiatric Disorders	4 (3.9)	3 (5.4)	(-8.4, 5.6)
Renal And Urinary Disorders	20 (19.6)	4 (7.1)	(2.2, 22.7)
Reproductive System And Breast Disorders	1 (1.0)	1(1.8)	(-4.8, 3.2)
Respiratory, Thoracic And Mediastinal Disorders	15 (14.7)	4 (7.1)	(-2.1, 17.2)
Skin And Subcutaneous Tissue Disorders	9 (8.8)	3 (5.4)	(-4.6, 11.5)
Vascular Disorders	10 (9.8)	6 (10.7)	(-10.9, 9.0)

A statistical difference was noted between DuraSeal Spinal Sealant and Control arms in two SOCs, "Injury, Poisoning and Procedural" and "Renal and Urinary Disorders".

A higher rate of events classified under the SOC of "Injury, Poisoning and Procedural Complications" was reported in the DuraSeal Spinal Sealant arm compared with the Control arm (43.1% vs. 12.5%; $p<0.001$). When evaluating the type of events included in this SOC for subjects treated with the DuraSeal Spinal Sealant, it is observed that there are numerous single reports for surgical related complications. The events include airway complication of anesthesia, corneal abrasion, fall, graft complication, positional injuries, nerve injury due to surgical manipulation, skin injury or laceration. The majority of these events (75%), were mild or moderate in nature which is similar to the proportion of mild to moderate events observed within this SOC for the Control arm (i.e., 77%). No adverse events in this SOC were considered related to device with the exception of one event of pseudomeningocele.

The largest category of events within this SOC of "Injury, Poisoning and Procedural Complications" reported for the DuraSeal Spinal Sealant arm is incision site complications (17 events total). Within this category are 10 reports of incisional pain noted post-operatively. These events were all non-serious and resolved without sequelae. The CEC attributed many of these observations to the normal post-operative surgical course and therefore considered the observation to be a non-event.

Also included under the "Injury, Poisoning and Procedure" SOC are post lumbar puncture syndrome, experienced by 4 DuraSeal Spinal Sealant subjects. There were 8 AEs of pseudomeningocele in the DuraSeal Spinal Sealant arm, 3 of which were pseudomeningocele responding to conservative therapy (Subjects 09-003, 15-008 and 21-003), and therefore, not

protocol defined endpoint CSF leaks. All of these events resolved without further surgical intervention.

Another System Organ Class notable for a statistical difference between the DuraSeal Spinal Sealant and the Control arms is "Renal and Urinary Disorders" (19.6% vs. 7.1% respectively; p=0.039). A majority of the events reported in the DuraSeal Spinal Sealant arm were urinary retention, specifically in 13 subjects (12.7%). All subjects experiencing urinary retention in the Spinal Sealant group underwent excision of a spinal tumor or cyst. In 8 of the Spinal Sealant subjects, the study procedure level was within the thoracic or cervical regions. Urinary retention is a common post-operative complication following surgery, and specifically, has been reported with a frequency of 23.6% for patients undergoing spine surgery.

Serious Adverse Events

The nature and incidence of serious adverse events are comparable between the two treatment arms. Within system organ classes, there were no statistically significant differences in the rates of events. Table 13 Serious Adverse Events Presented by SOC and Preferred Term.

Table 13 Serious Adverse Events Presented by SOC and Preferred Term

System Organ Class/ Preferred Term	DuraSeal Spinal Sealant (N=102)	Control (N=56)
Any Serious Adverse Event	**30 (29.4)**	**10 (17.9)**
Gastrointestinal Disorders	3 (2.9)	2 (3.6)
Diverticular Perforation	1 (1.0)	0 (0.0)
Gastric Ulcer Haemorrhage	0 (0.0)	1 (1.8)
Nausea	0 (0.0)	1 (1.8)
Pancreatitis	1 (1.0)	0 (0.0)
Vomiting	1(1.0)	0 (0.0)
General Disorders And Administration Site Conditions	1 (1.0)	0 (0.0)
Pyrexia	1 (1.0)	0 (0.0)
Infections And Infestations	1 (1.0)	2 (3.6)
Clostridium Difficile Colitis	0 (0.0)	1 (1.8)
Diverticulitis	1 (1.0)	0 (0.0)
Urinary Tract Infection	0 (0.0)	1 (1.8)
Injury, Poisoning And Procedural Complications	16 (15.7)	3 (5.4)
Graft Complication	1 (1.0)	0 (0.0)
Incision Site Complication (2)	5 (4.9)	1 (1.8)
Nerve Injury	1 (1.0)	0 (0.0)
Post Lumbar Puncture Syndrome	2 (2.0)	0 (0.0)
Pseudomeningocele (3)	5 (4.9)	3 (5.4)
Subdural Hematoma	1 (1.0)	0 (0.0)
Wound Dehiscence (3)	1 (1.0)	0 (0.0)

Musculoskeletal And Connective Tissue Disorders	1 (1.0)	0 (0.0)
Mobility Decreased	1 (1.0)	0 (0.0)
Neoplasms Benign, Malignant And Unspecified (Including Cysts And Polyps)	1 (1.0)	0 (0.0)
Brain Cancer Metastatic	1 (1.0)	0 (0.0)
Nervous System Disorders	9 (8.8)	1 (1.8)
Cerebrospinal Fistula [3]	2 (2.0)	0 (0.0)
Headache	1 (1.0)	0 (0.0)
Loss Of Proprioception	1 (1.0)	0 (0.0)
Paralysis	1 (1.0)	0 (0.0)
Paraplegia	1 (1.0)	0 (0.0)
Radiculopathy	1 (1.0)	0 (0.0)
Sensory Loss	1 (1.0)	1 (1.8)
Syncope Vasovagal	1 (1.0)	0 (0.0)
Renal And Urinary Disorders	2 (2.0)	2 (3.6)
Nephrolithiasis	0 (0.0)	1 (1.8)
Renal Failure	0 (0.0)	1 (1.8)
Urinary Retention	2 (2.0)	0 (0.0)
Respiratory, Thoracic And Mediastinal Disorders	3 (2.9)	2 (3.6)
Pulmonary Embolism	1 (1.0)	2 (3.6)
Respiratory Failure	2 (2.0)	0 (0.0)
Vascular Disorders	1 (1.0)	1 (1.8)
Deep Vein Thrombosis	1 (1.0)	1 (1.8)

(1) MedDRA preferred terms including events of deep SSI
(2) MedDRA preferred terms including events of endpoint CSF leaks
(3) MedDRA preferred terms including events of endpoint CSF leaks

Neurological Evaluations

All subjects were to undergo neurological, cranial nerve, motor, sensory, and reflex examinations at baseline and each post-operative assessment time point. Additionally, subjects underwent gait and ankle clonus evaluations; and assessment of radicular pain. Radicular pain was to serve as an indicator for evaluation of nerve root compression. Furthermore, any changes from baseline (new or worsening deficits) were recorded as adverse events. There were no significant differences between the two treatment arms with respect to the proportion of events categorized as nervous system disorders.

Overall the types of changes in neurological status reported below are consistent and expected for the Study population, and, in review of the post-operative course for subjects treated with the DuraSeal Spinal Sealant there do not appear to be any evidence of symptom complexes consistent with nerve root compression.

Neurological Assessment

The neurological assessment includes evaluation of vital sign instability, level of consciousness, personality changes, speech disorder and visual changes, rating responses as normal, slightly abnormal, moderately abnormal, severely abnormal, or unable to measure or missing. There were no significant differences within the arms related to shift status from the baseline assessment to each post-baseline assessment for each component of the neurological assessment.

Cranial Nerve Assessments

Cranial nerves (CII through CXII) were assessed as normal or abnormal. There were no significant differences in shift status within treatment arms from baseline to each post-baseline assessment with respect to cranial nerve evaluation.

Motor Exam

Bilateral motor examinations of the lower and upper extremities were evaluated as normal or abnormal. Significant improvements in status from baseline were observed for the Control arm for the following assessments: right upper extremities (p-value (30-day) = 0.0455, p-value (90-days) = 0.0253) and left lower extremities (p-value (30-day) = 0.0253).There were no statistically significant changes in status from baseline for the DuraSeal Spinal Sealant arm.

Sensory Exam

Bilateral sensory examinations of the lower and upper extremities were evaluated as normal or reduced. Significant improvements from baseline in right lower extremities
(p-value (30-day) = 0.0073, p-value (90-day) = 0.0029) were observed in the DuraSeal Spinal Sealant arm, and significant changes from baseline in the left lower extremities
(p-value (30-day) = 0.0455, p-value (90-day) = 0.0253) in the Control arm.

Deep Tendon Reflex Assessment

Deep tendon assessments included bilateral evaluation of the biceps, triceps, knee jerk and ankle jerk with reflex assessed as normal, decreased or brisk. For the DuraSeal Spinal Sealant arm, all but one parameter, the right knee jerk, demonstrated significant improvements from baseline to the discharge assessment. For the Control arm, there were significant improvements from baseline to the discharge assessment for all parameters. At the 30 day visit, there were significant improvements within the DuraSeal Spinal Sealant arm for all measured parameters and, within the Control arm, there were significant improvements for left and right ankle jerk. At the 90 day visit, there were significant improvements within the DuraSeal Spinal Sealant arm for all measured parameters, with the exception of right biceps, but there were none within the Control arm. Overall, there was more improvement for the DuraSeal Spinal Sealant arm than for the Control arm.

Other Neurological Outcomes: Radicular Pain, Ankle Clonus and Gait

At the baseline and post-baseline visits, each subject was evaluated for the presence of radicular pain (yes/no), ankle clonus (yes/no) and gait (rated normal or abnormal). Both treatment arms experienced significant changes from baseline to the 90-day evaluation in the presence of radicular pain (DuraSeal Spinal Sealant p= 0.0000; Control p= 0.0005). This change was in the

direction of improvement, as a majority of subjects with radicular pain at baseline were normal at the 90-day evaluation. Indeed, whereas, approximately 30% of subjects within both arms were suffering with radicular pain at baseline, at the 90 day assessment the proportion of subjects experiencing radicular pain was reduced to approximately 10% or less. Similar results were observed for the presence of ankle clonus, as most subjects were back to normal at the 90-day exam. There were no significant changes in evaluation of subject gait, with the exception of a significant improvement in the DuraSeal Spinal Sealant arm at 90 days (p=0.0116).

Clinical Laboratory Evaluation

All subjects underwent a full battery of laboratory testing, including hematology minus differentials (WBC, RBC, Hemocrit (HCT), Hemoglobin (HgB), Platelet count), Electrolytes (Na, K, Cl, CO_2), Renal Function (Blood Urine Nitrogen (BUN), Creatinine), Liver Function (alkaline phosphatase, Total Bilirubin, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Albumin and Glucose at the baseline assessment. Additionally, a baseline pregnancy test was required for female subjects of child-bearing potential. At the discharge assessment, all but the albumin, electrolyte panel and glucose tests were performed. At the 30 and 90 day visits all laboratory testing was repeated with the exception of the albumin evaluation. Sites were instructed to indicate whether specific tests results were outside the normal range (based on the normal ranges established for the site's testing laboratory) and if so, whether the deviation from normal represented a clinically significant change. Any out of normal range results determined to be clinically significant were to be documented as adverse events.

Evaluation of Each Laboratory Parameter

Laboratory Values Over Time

The mean and median changes over time were small and not clinically relevant. Sporadic low and high laboratory values were noted for the majority of the analytes; however, no patterns of change were observed for any analyte for either treatment arm.

Several subjects had shifts from normal at baseline to a low or high value at the end of treatment. All adverse laboratory events were non-serious, mild to moderate and all resolved. Events of increased blood sugar were most commonly due to steroid use during the peri-operative time period.

Clinically Significant Abnormalities

All abnormal laboratory values that were determined to be clinically significant by the investigator were reported as adverse events (e.g., electrolyte disturbances, blood glucose increased, anemia and leukocytosis). These events are categorized in System Organ Classes: Blood and Lymphatic System Disorders, Investigations, and Metabolism and Nutrition Disorders. There were no statistically significant differences between the two arms for these System Organ Classes. None of the adverse events related to clinically significant laboratory values were deemed to be related to the DuraSeal Spinal Sealant.

Wound Healing

Overall by the 30 day evaluation, 96.0% of the DuraSeal Spinal Sealant subjects and 94.5% of the Control subjects were considered by the examiner to have a well healed surgical wound. By the 90 day follow-up, all wounds were well healed, with the exception of one subject in the DuraSeal Spinal Sealant arm (Subject 14-006), whose wound was partially healed. This subject experienced a superficial surgical site infection approximately 25 days post-operatively, which later developed into a deep surgical site infection. She was treated with antibiotics over the course of many weeks. At the 90 day evaluation, her incision remained open approximately 1cm at the very distal end. It was superficial, clean and showed no evidence of infection.

Vital Signs and Physical Examinations

Sporadic high and low values were observed in both treatment arms. No clinically significant patterns were noted within either treatment arm. Physical examination data are summarized as normal or abnormal status at each visit, as well as shifts in status from baseline to each follow-up visit. No clinically meaningful changes were observed. Changes from baseline status were significant in the DuraSeal Spinal Sealant arm for General Appearance (p= .0339 at discharge and p=0.0143 at 90 days) and the Musculoskeletal Exam (p=.0348 at discharge). If both cases, the shift was towards improvement.

Clinical Events Committee (CEC) Summary

During the course of the Study, the Clinical Events Committee (CEC) reviewed all reported adverse events. Their associated adjudications were made after a review of subject medical records. The CEC's observed that within each treatment arm, the observed events appeared consistent in type and severity for the Study population. The CEC did not recommend any modifications to the device or investigational plan.

Other Data Analysis

At each visit including baseline, 30 day and 90 day, all subjects were required to complete an SF-36v2™ Health Survey 1996, 2000 licensed by Quality Metric Incorporated and Medical Outcomes Trust Visual Analog Scales.

SF- 36 Health Transition Score

At the baseline visit, 14.6% of DuraSeal Spinal Sealant subjects reported that their health was "much worse than one year ago", while 8.9% of Control subjects reported the same. At 30 days, the percentages decreased to 7.4% of DuraSeal Spinal Sealant and 3.7% of Control subjects demonstrating a similar relative reduction in proportion of subjects who believed that they were in worse health. In fact, approximately 36% of DuraSeal Spinal Sealant and 46% of Control subjects reported their health much better or somewhat better than one year ago. At the 90 day evaluation, 49% of DuraSeal Spinal Sealant subjects and 52% of Control subjects reported their health as much better or somewhat better than one year ago. In summary, the results of the SF-36 questionnaires are comparable between the Study arms.

Visual Analog Pain Score

All subjects were required to rate their pain at baseline and again at the 30 and 90 day assessment using a Visual Analog Scale (VAS) from 0 to 10 at baseline, where 0 equals no pain and 10 equals worst possible pain. Mean VAS scores were comparable between the two Study arms. Within each treatment arm, pain levels decreased at the post-baseline assessments. The mean (± SD) change scores at 30 days are -2.2 ± 3.59 and -1.5 ± 3.74 for the DuraSeal Spinal Sealant and Control arms respectively. At 90 days the mean change scores from baseline are -2.1 ± 3.70 and -2.7 ± 3.73 for the DuraSeal Spinal Sealant and Control arms. The VAS pain change scores were comparable between the two Study arms. A change score of 1.4 or more units is generally recognized as a clinically meaningful improvement.

2. Effectiveness Results & Subgroup Analyses

Effectiveness Results

Following dural repair, subjects were assessed for intra-operative eligibility, including an evaluation of the primary dural repair for watertight closure. If a leak was observed, the nature of the leak was documented (i.e., spontaneous CSF leakage or leak upon Valsalva). Subjects were randomized if there was a spontaneous expression of CSF (no need for Valsalva) or non-watertight closure upon Valsalva. The nature of the baseline non-watertight closure was similar between both arms. Specifically 26.5% (Sealant) vs. 26.8% (Control) of subjects experienced spontaneous expression of CSF, and 73.5% (Sealant) vs. 73.2% (Control) experienced a non-watertight closure upon Valsalva following primary dural repair.

Within the DuraSeal Spinal Sealant arm, following the first application, 93 subjects (91.2%) had a watertight closure upon Valsalva. The 9 subjects with a non-watertight closure were treated with a second application of the hydrogel Sealant and all had a watertight closure upon second post-treatment Valsalva. All 102 subjects (100%) treated with the hydrogel Sealant met the criteria for primary endpoint success, i.e. intra-operative sealing.

Within the Control arm, 35 subjects (62.5%) had a watertight closure upon Valsalva following the first Standard of Care application. In one subject, no Control attempt was made and no additional Valsalva performed. Of the 20 subjects remaining with a non-watertight closure, 4 subjects received a second attempt of Standard of Care methods and only one of those subjects achieved a watertight closure upon second post-treatment Valsalva.

Of the 56 subjects in the Control arm, three (3) subjects were considered not evaluable for purposes of the primary effectiveness analysis, as the treating investigator chose not to use any protocol defined Standard of Care method to achieve watertight dural closure.

Two primary efficacy analyses were performed:

Intent to Treat Population (n = 158):

DuraSeal Spinal Sealant = 102 successes (100%); the 95% confidence interval for the true

percent of successes is 96.4% to 100%

Standard of Care = 36 successes (64.3%); the 95% confidence interval for the true percent of successes is 50.4% to 76.6%.

Per Protocol Population (n = 155):
DuraSeal Spinal Sealant = 102 successes (100%); the 95% confidence interval for the true percent of successes is 96.4% to 100%

Standard of Care = 36 successes (67.9%); the 95% confidence interval for the true percent of successes is 53.7% to 80.1%

In both efficacy analyses performed, the difference between arms in primary endpoint success was highly significant with a p-value <0.001.This satisfied the success criterion for the study.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

European Pilot Study

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 CSF leakage following dural Sealant application, defined as no CSF leakage from the dural repair intra-operatively 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.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on May 14, 2009 the Neurological Devices Devices Panel[1] recommended that the Covidien PMA, P080013, for the DuraSeal Spine Sealant System PMA be conditionally approved subject to the following conditions:

1. A post-approval study to evaluate the incidence of infection and CSF leak rates associated with use of the device.

2. A revised product labeling to include the following:
   - Revise contraindication to a label warning and state; DuraSeal can swell after application, it should not be used in areas where neural structures could be compressed'.
   - No difference in the prevention of long term CSF leakage has been demonstrated and standard diligence in wound closure should be carried out when using this device.

1. http://origin.www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/ucm152403.htm

B. FDA's Post-Panel Action

On the basis of preclinical and clinical testing data provided in the PMA, coupled with the proposed post approval study, and taking into account the panel's recommendation, FDA determined that the sponsor had demonstrated a reasonable measure of safety and effectiveness and found the subject device approvable with conditions.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety & Effectiveness Conclusions

In summary, the types of adverse events observed in both of the Study treatment arms were anticipated, given the medical conditions of the enrolled subjects and nature of the neurosurgical procedures performed. There were no deaths or unanticipated adverse device effects observed in the Study. No events were deemed related to the device per the independent CEC.

The incidence of protocol defined post-operative CSF leaks was comparable between the two treatment arms (7.8% vs. 5.4%, p= 0.748). The Study protocol allowed surgeons to utilize "rescue" therapy to ensure that the dura was closed intra-operatively watertight prior to wound closure, even if the assigned treatment (DuraSeal Spinal Sealant or Control) failed. In 100% of subjects treated with the DuraSeal Spinal Sealant, a watertight dural closure was achieved. While the rate of intra-operative dural sealing after application of the chosen Control method was 64.3%, in all cases, the investigator

went on to apply "rescue" therapy to ensure the subject's dura was watertight prior to wound closure.

Based on the CDC criteria, the incidence of post-operative SSIs was also comparable between the two arms (6.9% and 7.1% of subjects in the DuraSeal Spinal Sealant and Control arms, respectively, p=1.00). One of the deep surgical site infections occurred in a subject whose glucose was not controlled at the time of Study inclusion (recorded as 280 mg/dL at baseline and 30 day glucose was 292 mg/dL). Another subject had undergone revision surgery for displacement of a lumbar interbody fusion device ("cage"). Furthermore, for another subject within the DuraSeal Spinal Sealant arm who reportedly had a superficial SSI (described as a "crusty lesion" with no confirmation of infection), the CEC did not agree with the investigator's assessment that this was an adverse event at all, yet alone a superficial SSI. If these subjects were excluded from the analysis, the incidence of all infections in the DuraSeal Spinal Sealant arm remains lower than that of the Control arm (3.9% vs. 7.1% respectively) and the frequency of deep surgical site infections would be similar (2.9% vs. 1.8% respectively).

There were no statistically significant differences in incidence of AEs within SOCs between groups with two exceptions. A majority of the adverse events reported were consistent between arms at the System Organ Class level. There were two SOCs in which there was a statistical difference in the sealant arm, "Injury, Poisoning, and Procedural Complications" and "Renal and Urinary Disorders". While the reason for the overall difference is not clear, a majority of the events observed within the DuraSeal Spinal Sealant arm were mild to moderate in severity (75%), resolved in most cases without sequalae, and were not deemed to be related to the device

Overall, there were no clinically relevant differences in safety outcomes between the two treatment arms (DuraSeal Spinal Sealant vs. Control) with respect to laboratory evaluations, neurological exams, vital signs, physical examination and wound healing.

B. **Overall Conclusions**

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

Preclinical studies were conducted to evaluate product safety and included biocompatibility and toxicology studies. Device safety and effectiveness was also assessed in animal models. Product specifications have been identified and validated to ensure the manufacture of product of consistent quality. The specifications are product benchmarks that assess product characteristics which are essential to device performance.

The clinical study observed a 100% rate of watertight closure as tested by a Valsalva maneuver to 20-25 cm of water pressure after DuraSeal Spine Sealant application. The results demonstrate that the device is effective as an adjunct to suturing in providing an intra-operative water-tight dural closure. The types of adverse events observed in both of

the Study treatment arms were anticipated, given the medical conditions of the enrolled subjects and nature of the neurosurgical procedures performed. There were no deaths or unanticipated adverse device effects observed in the Study. No events were deemed related to the device per the independent CEC. Further evaluation of risk factors for these events will be assessed in the post-approval study.

In conclusion, the Spinal Sealant System has been established to be safe and effective for providing a watertight closure when used as an adjunct to sutured dural repair during spinal surgery. This Spinal Sealant will provide neurosurgeons with a readily available tool for constructing watertight dural repairs, where currently no approved product exists. The use of DuraSeal Sealant may minimize the off-label use of other commonly applied technologies which have not been established to be either safe or effective as an adjunct to sutured dural repair during spine surgery.

XIV. CDRH DECISION

CDRH issued an approval order on September 4, 2009. The final conditions of approval cited in the approval order are described below.

In addition to the post-approval requirements outlined in the enclosure, the sponsor agreed to the conditions of approval, including performing a post-approval study, as described in items below and the post-approval study outlines sent by the sponsor to the Division of Epidemiology via email on July 17, 2009.

The post-approval study is a multi-center, non-randomized study with a prospective DuraSeal treatment arm and a retrospective standard of care control arm, designed to estimate the rates of post-operative CSF leak, deep surgical site infection (DSSI), and neurological Serious Adverse Events (SAEs) at 90 days for the DuraSeal Spinal Sealant arm and compare these rates to the corresponding rates for the control arm. The DuraSeal Spinal Sealant Prospective Treatment arm will enroll 305 subjects from up to 40 sites within the United States. Subjects undergoing spinal surgery where there is a possibility of opening of the dura (either intentional or incidental) will be consented prior to surgery. The Retrospective Standard of Care Control arm will enroll 683 subjects identified in a retrospective review of medical charts at the same study centers for a pre-defined time period (1 year) as patients who have undergone a spinal procedure and received treatment for an opening of the dura (either intentional or incidental). All cases that meet eligibility criteria within the pre-specified time period will be included. For both arms, you have agreed to collect information about patient demographic, medical history and documented procedural data (such as Indication for surgery, procedure(s) performed, level(s) of surgery, surgical approach, dural opening details, other control products, etc.) You also agreed to collect information documenting the incidence of CSF Leak, DSSI, and all neurosurgical SAEs at 90-days post-operation. The primary hypothesis to be tested in this study is the non-inferiority of DuraSeal Spinal Sealant to control treatment with respect to CSF leakage at 90-day post-procedure using a non-inferiority margin of 5% after accounting for the potential imbalance between the two

groups on confounders of the relationship between treatment for a dural opening and CSF leakage.

Every six months for the first two years and then annually until the study is completed sponsor will submit a progress report to the FDA that includes, but is not limited to, the status of site enrollment, the status of patient enrollment, the status of patient follow-up, and other milestones as it compares to the stated goals in the protocol and an explanation for a delay, if any in meeting these goals, and the safety and effectiveness data collected during that reporting period.

Sponsor will also update patient and physician labeling (via a PMA supplement) to reflect the findings in the PAS, as soon as these data are available, as well as any other timepoint deemed necessary by FDA if significant new information from this study becomes available.

Sponsor was also advised to submit a full post-approval study protocol in a PMA Supplement and reach agreement with OSB on the protocol within 30 days after the approval order is issued and that FDA would act on and respond to the sponsor's protocol submission within 60 calendar days of receipt.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.