2009-4437b1-04

Proposed Summary of Safety and Effectiveness

4.0 SUMMARY OF SAFETY AND EFFECTIVENESS DATA

4.1 GENERAL INFORMATION

Device Generic Names:	Surgical Sealant, Polymerizing
Device Trade Names:	DuraSeal Xact Sealant System
Applicant's Name and Address:	Confluent Surgical, Inc. 101A First Avenue Waltham, MA 02451, USA
PMA Number:	TBD
Date of Panel Recommendation:	TBD
Date of Notice of Approval to the Applicant:	TBD

4.2 INDICATIONS FOR USE

The DuraSeal Xact Sealant System is intended for use as an adjunct to sutured dural repair to obtain watertight closure during spinal surgery.

4.3 DEVICE DESCRIPTION

The DuraSeal Xact 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 Xact Sealant produced by the DuraSeal Xact 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. 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 Xact Sealant can be used for up to one hour following reconstitution.

The DuraSeal Xact 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).

4.4 CONTRAINDICATIONS

The DuraSeal Xact Sealant is contraindicated for use as a void filler in enclosed spaces in the spine (such as the lateral gutters and neural foramen), as post-operative hydrogel swelling may impinge on surrounding tissues.

4.5 WARNINGS AND PRECAUTIONS

Warnings

- The safety and effectiveness of the hydrogel sealant has not been studied in:
  - Patients with a known allergy to FD&C Blue #1 dye.
  - Procedures involving non-autologous duraplasty material.
  - Patients with severely altered renal or hepatic function
  - Patients with a compromised immune system or autoimmune disease
- Do not use if an active infection is present at the surgical site.
- Do not use the hydrogel sealant as a hemostatic agent

Precautions

- Use only with the Confluent Surgical applicators
- The polymer kits and applicators are provided sterile. Do not use if packaging or seal has been damaged or opened. Do not re-sterilize.
- The polymer kits and applicators are intended for single use only. Discard opened and unused product.
- Do not use if the PEG powder is not free flowing.
- Use within 1 hour of polymer preparation
- Do not use in combination with other sealants or hemostatic agents.
- Do not use in patients younger than 18 years of age, or in pregnant or breastfeeding females.

- Prior to application of the hydrogel sealant, ensure that adequate hemostasis has been achieved.
- Incidental application of the hydrogel sealant to tissue planes that will be subsequently approximated, such as muscle and skin, should be avoided.

4.6 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, fat grafts,surgical hemostatic agents, and/or fibrin glue.

4.7 MARKETING HISTORY

The DuraSeal Xact Sealant System, 5 mL kit configuration 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, 5 ml kit configuration, 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 Xact 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.

Table 4-1 identifies the countries where the DuraSeal Xact Sealant System and DuraSeal Dural Sealant System are approved for commercial sale.

Table 4-1 Country Approvals

DuraSeal Xact Sealant System (2ml kit)
Country
European Union
Middle East Countries*
Australia/New Zealand
South Africa
DuraSeal Dural Sealant System (5ml kit)
European Union
Middle East Countries*
Australia / New Zealand
Canada
South Korea

*Middle East Countries consist of Israel, Jordan, Saudi Arabia, Kuwait, Turkey, Egypt, Lebanon, Syria, Iran, UAE, Bahrain, Oman, Quatar (DuraSeal Only)

4.8 POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

In the pivotal clinical study, 102 patients were treated with the DuraSeal Xact 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.

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 4-2. Adverse Events by System Organ Class

System Organ Class	DuraSeal Xact Sealant (N=102) n (%)	Control (N=56) n (%)	p-value[1]
Any Adverse Event	95 (93.1)	51 (91.1)	0.755
Blood And Lymphatic System Disorders	10 (9.8)	4 (7.1)	0.772
Cardiac Disorders	10 (9.8)	2 (3.6)	0.216
Eye Disorders	6 (5.9)	1 (1.8)	0.423
Gastrointestinal Disorders	21 (20.6)	9 (16.1)	0.532
General Disorders And Administration Site Conditions	33 (32.4)	18 (32.1)	1.000
Immune System Disorders	1 (1.0)	0 (0.0)	1.000
Infections And Infestations	19 (18.6)	9 (16.1)	0.828
Injury, Poisoning And Procedural Complications	44 (43.1)	7 (12.5)	<0.001
Investigations	50 (49.0)	23 (41.1)	0.405
Metabolism And Nutrition Disorders	10 (9.8)	3 (5.4)	0.384
Musculoskeletal And Connective Tissue Disorders	24 (23.5)	15 (26.8)	0.701
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	4 (3.9)	0 (0.0)	0.298
Nervous System Disorders	48 (47.1)	21(37.5)	0.315
Psychiatric Disorders	4 (3.9)	3 (5.4)	0.699
Renal And Urinary Disorders	20 (19.6)	4 (7.1)	0.039
Reproductive System And Breast Disorders	1 (1.0)	1(1.8)	1.000
Respiratory, Thoracic And Mediastinal Disorders	15 (14.7)	4 (7.1)	0.206
Skin And Subcutaneous Tissue Disorders	9 (8.8)	3 (5.4)	0.541
Vascular Disorders	10 (9.8)	6 (10.7)	1.000

(1) p-value from Fisher's Exact test for a difference between treatment groups in the percentages of patients experiencing at least one AE in that given system organ class.

A statistically significant higher rate of events classified under "Injury, Poisoning, and Procedural Complications" were reported in the DuraSeal Xact group compared with the Control group. When evaluating the type of events included in this category for patients

treated with the DuraSeal Xact Sealant, it is observed that there are numerous single reports for surgery related complications that cannot reasonably be attributed to the hydrogel sealant. The events include, amongst others, airway complication of anesthesia, corneal abrasion, fall, graft complication, positional injuries, nerve injury due to surgical manipulation, skin injury or laceration. Also included in this category are reports of incisional pain, post-lumbar puncture syndrome after removal of intra-operatively placed lumbar drain, and pseudomeningocele responding to conservative therapy.

A statistically significant higher rate of events classified under "Renal and Urinary Disorders" were reported in the DuraSeal Xact Sealant group compared with the Control group. The majority of the events reported in the DuraSeal Xact Sealant group were urinary retention. Of note, all patients experiencing urinary retention underwent excision of a spinal tumor or cyst. More than half of these patients had surgery within the thoracic or cervical regions; and therefore it is unlikely that sealant application is associated with the observed urinary complications, as bladder function is controlled at lower dermatome levels (i.e., lumbosacral). Urinary retention is a common post-operative complication following spine surgery.

4.9 SUMMARY OF PRE-CLINICAL STUDIES

4.9.1 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 (reference **Table 4-3**) 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 4-3 Summary of DuraSeal Xact 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

Test Reference	Method Reference	Results
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
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.

4.9.2 *In Vitro* Product Testing

A series of *in vitro* tests were performed on the components and materials of the DuraSeal Xact Sealant System (final, sterilized devices). In addition to the studies identified in **Table 4-4** environmental testing was performed to assure that the product is not affected by temperature extremes or maximum irradiation dose.

Table 4-4 *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 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%.
In vitro absorption – disappearance	Hydrogel time of dissolution when placed in Phosphate Buffered Saline (PBS) at 60.4 °C.	DuraSeal Xact 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.

4.9.3 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*".

4.9.4 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

4.9.5 Animal Testing

A series of animal studies were conducted to evaluate the *in vivo* performance and safety of the DuraSeal Xact Sealant System. **Table 4-5** provides a summary of the tests performed and the relevant findings.

Table 4-5. 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 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 groups 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 group. 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-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 MR and 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,

Test Performed	# Animals/ Study Duration	Summary/Relevant Findings
		14, 28, and 42 post-treatment. At days 4 and 42 after implantation, four animals per treatment group 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 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.
Evaluation of Hydrogel Persistence Following Subcutaneous Implantation in the Rat	21 test (hydrogel) and 21 control/14 weeks	The 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. 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.
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 histopathology. None of the animals[1] 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.
Cauda Equina Study in the Canine	9 animals each assigned to treatment group (hydrogel) or surgical control (no	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

[1] One animal developed an infection three days after surgery and had to be euthanized.

Test Performed	# Animals/ Study Duration	Summary/Relevant Findings
	treatment)/8 weeks.	weeks. Wound healing, tissue response, scar formation and nerve root mobility were evaluated using gross dissection and histopathology. The 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.

4.9.6 Dye Toxicology Evaluations

The DuraSeal Xact 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 (21 CFR 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 Xact 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.

4.10 SUMMARY OF CLINICAL STUDIES

A prospective, multi-center, randomized, two-arm, single blind clinical investigation was conducted to evaluate the safety and effectiveness of the DuraSeal Xact 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 102 subjects were treated with the DuraSeal Xact Sealant, and a total of 56 subjects were treated using Standard of Care (Control) methods.

Inclusion/Exclusion criteria for the study included the following:

Pre-Operative Inclusion Criteria:

- Subject is between 18 and 75 years of age
- Subject is scheduled for a spinal procedure that entails a dural incision.
- Subject requires a procedure involving surgical wound classification Class I/Clean
- Subject or authorized representative, has been informed of the nature of the study, and has provided written informed consent, approved by the appropriate Institutional Review Board (IRB) of the respective clinical site

Pre-Operative Exclusion Criteria:

- Subject had active spinal and/or systemic infection.
- Subject required additional spine surgery within the study time period.

- Subject had a previous spinal surgery involving dural exposure and/or entry at the same level(s) as the study procedure.
- Subject had pre-existing external lumbar CSF drain or internal CSF shunt.
- Subject participated in a clinical trial of another investigational device or drug.
- Subject with creatinine > 2.0 mg/dL.
- Subject with total bilirubin > 2.5 mg/dL.
- Pregnant or breast-feeding females or females who wished to become pregnant during the length of study participation.
- Subject treated with chronic steroid therapy unless discontinued more than 6 weeks prior to surgery (standard peri-operative steroids are permitted). For purposes of this protocol, chronic steroid therapy is defined as greater than 4 weeks.
- Subject had documented history of significant coagulopathy with a PTT > 35 sec, PT/ INR >1.2, receiving aspirin, or NSAIDS at the time of surgery. Note: Subjects who are receiving cardiovascular prophylaxis are not excluded.
- Subject received warfarin or heparin at the time of surgery (including analogs).
- Subject diagnosed and documented compromised immune system and/or autoimmune disease.
- Subject had chemotherapy treatment within 6 months prior to, or planned during the study (until completion of last follow-up evaluation).
- Subject had prior radiation treatment to the surgical site or has planned radiation therapy within 30 days post procedure.
- Subject had a known malignancy or another condition with prognosis shorter than 6 months.
- Subjects with documented history of uncontrolled diabetes.
- The investigator determined that the subject should not be included in the study for reason(s) not already specified.

Intra-Operative Inclusion Criteria:

- Presence of non-watertight dural closure, either spontaneously or upon Valsalva maneuver to 20 - 25 cm H_2O for 5-10 seconds

Intra-Operative Exclusion Criteria:

- Subject required use of synthetic or non-autologous duraplasty material
- Subject has a gap greater than 2 mm remaining after primary dural closure
- Subject has undergone laminoplasty decompression
- Subject has undergone a syringomyelia procedure where the shunt is not placed in the subarachnoid position
- Subject has undergone a Chiari malformation procedure that does not entail a dural incision at or below the C1 level
- Incidental finding of any of the Pre-operative Exclusion Criteria
- Investigator determines that participation in the study may jeopardize the safety or welfare of the subject

Safety and Effectiveness Parameters:

The primary effectiveness endpoint for the study was the percent success in obtaining a watertight closure following assigned treatment (DuraSeal Xact Sealant or Standard of

Care). 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.

Treatment and Follow-Up Procedures

Prior to initiation of enrollment, all study surgeons were trained on the proper use of the DuraSeal Xact 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 Xact 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 Xact 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 scales (VAS) and quality of life self-assessments (SF-36). Additionally, any reported adverse events were documented for each of the assessment intervals.

Subject Accountability and Demographics

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 Xact Sealant System and 56 subjects were treated using Standard of Care methods. Of the 158 subjects, 153 subjects (96%) completed the three-month follow-up visit. Subject demographics are provided in Table 4-6.

Table 4-6. Subject Demographics

[illegible]	[illegible]	[illegible]
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)
[redacted]		
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)

Efficacy Evaluation

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 groups. 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.

Following the first hydrogel sealant 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 group, 35 subjects (62.5%) had a watertight closure upon Valsalva following the first Standard of Care application. In one subject, no post-treatment Valsalva was completed as no Standard of Care attempt was made. Of the 20 subjects 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 group, 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):
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):
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 groups in primary endpoint success was highly significant with a p-value <0.001; therefore, the success criterion for the study has been satisfied.

Safety Evaluations

Safety of the DuraSeal Xact 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.

There were no deaths or unanticipated adverse device effects observed in the study. The number and types of adverse events observed (see **Table 4-2**) in both study treatment groups were anticipated, given the medical conditions of the treated subjects and the nature of the complex neurosurgical procedures performed. Overall, 29.4 % of subjects in the DuraSeal Xact Sealant group and 17.9% of subjects in the Control group experienced at least one SAE.
There were no unanticipated adverse device effects noted for either treatment group and only one subject within the Spinal Sealant group (1.0%) was noted to have a device-related event as determined by the investigator.

The incidence of protocol defined post-operative CSF leaks was comparable between the two treatment groups: Spinal Sealant 7.8% vs. Control 5.4% (p= .0748) or the time to CSF leak onset (p=0.578, log rank test). The incidence of surgical site infections was also comparable between the two groups: Spinal Sealant 6.9% vs. Control 7.1% (p=1.000). Refer to Table 4-7 and Table 4-8 for further breakdown of the observed post-operative CSF Leaks and Surgical Site Infections.

Table 4-7 – Incidence of Post-operative CSF Leaks

Category	Statistic	Spinal Sealant (N=102)	Control (N=56)	p-value [1]
Presence of endpoint CSF leak within 90 days post-procedure	**n (%)**	**8 (7.8)**	**3 (5.4)**	0.748
CSF Fistula	**n**	**3**	**0**	
Pseudomeningocele	**n**	**5**	**3**	

Table 4-8 – Incidence of Post-operative Surgical Site Infection

Category	Statistic	Spinal Sealant (N=102)	Control (N=56)	p-value [1]
Presence of SSI within 90 days post-procedure	n (%)	7 (6.9)	4 (7.1)	1.000
Deep Surgical Site Infection	n	5	1	
Superficial Surgical Site Infection	n	2	3	

There were no clinically relevant differences in safety outcomes between the two treatment groups with respect to laboratory evaluations, neurological exams, vital signs, physical examination and wound healing. In evaluation of the neurological assessment data and neurological complications, there is no indication of symptom complexes consistent with nerve root compression for subjects treated with the Spinal Sealant, a potential concern when using hydrogel-based devices along the nerve roots. There was no statistical difference in the incidence of serious adverse events (SAEs) between the two groups; Spinal Sealant 29.4% vs. Control 17.9% (p=0.11). Overall, the adverse event profile for subjects treated with the Spinal Sealant was similar to that of the Control group within the majority of System Organ Classes (SOCs). Where differences were noted, reports within the Spinal Sealant group were consistent in nature and severity for this study population, a population undergoing complex neurosurgical procedures. There were no unexpected findings relative to the safety assessment of the Spinal Sealant.

Additionally in this study, there was no association between the application of larger volumes of sealant, assessed as the total volume of material applied and as volume normalized for the length of the dural incision, and key neurological safety parameters including CSF leaks, surgical site infections or specific neurological complications.

4.11 CONCLUSIONS DRAWN FROM STUDIES

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 intra-operative watertight closure as tested by a Valsalva maneuver to 20-25 cm of H_2O after DuraSeal Xact Sealant application, compared to a 64.3% rate of watertight closure as tested by a Valsalva maneuver after Standard of Care application. The difference in rates of intra-operative watertight closure was highly significant with a p-value <0.001; therefore, the DuraSeal Xact Sealant has been demonstrated to be superior to the Standard of Care methods applied within the Control group for achieving a watertight dural repair. The results demonstrate that the DuraSeal Xact Sealant is effective at providing a watertight dural closure in cases where suturing alone, or in combination with autologous grafting is not successful. Achieving a watertight closure of the dura is recognized as an important step in preventing postoperative CSF leaks. Post-operative protocol defined CSF leaks occurred in 7.8% and 5.4% of subjects in the Spinal Sealant and Control groups respectively. This difference is not statistically significant (p=0.748, two sided Fisher Exact test). Surgical Site Infections (SSIs) occurred in 6.9% and 7.1% of subjects in the DuraSeal Xact Sealant and Control groups, respectively. This difference is not statistically significant (p=1.000, two sided Fisher Exact test). There were no deaths or unanticipated adverse device effects observed in the study. The number and types of adverse events observed (see **Table 4-2**) in both study treatment groups were anticipated, given the medical conditions of the treated subjects and the nature of the complex neurosurgical procedures performed.

In conclusion, results from preclinical studies indicate that the DuraSeal Xact Sealant System meets or exceeds safety and performance specifications. Data collected from a multi-center clinical investigation of the performance of the DuraSeal Xact Sealant System provides a reasonable assurance of product safety and effectiveness when the device is used, in accordance with the labeling, as an adjunct to sutured dural repair to provide watertight closure during spinal surgery.

Therefore, it is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

4.12 PANEL RECOMMENDATION

To Be Determined

4.13 CDRH DECISION

To Be Determined

4.14 APPROVAL SPECIFICATIONS

To Be Determined