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Sponsors Executive Summary

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Confluent Surgical (dba Covidien)

Sponsor Executive Summary for DuraSeal Spine Sealant, P080013

Center for Devices and Radiological Health (CDRH) Advisory Panel

May 14, 2009

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Appendix A: A Prospective, Multi-Center, Randomized Controlled Study to Compare the Spinal Sealant System as an Adjunct to Sutured Dural Repair with Standard of Care Methods during Spinal Surgery, Protocol DRS-05-001

Appendix B: DuraSeal Spine Sealant PMA, P080013, Amendment 1

Appendix C: DuraSeal Spine Sealant PMA, P080013, Amendment 2

1.0 EXECUTIVE SUMMARY

1.1 INTRA-OPERATIVE SPINAL DURAL SEALING

An effective means to create intra-operative watertight dural closure to prevent CSF leakage in cranial surgery became available with the commercial introduction of Covidien's DuraSeal® Dural Sealant System (PMA P040034; approved on April 7, 2005). The sponsor is now seeking premarket approval for use of the **identical** PEG-based hydrogel in patients undergoing procedures in the spine, so that physicians and their patients can realize the benefits of a watertight dural repair in these types of procedures. The DuraSeal Spine™ Sealant is intended for use as an adjunct to sutured dural repair during spinal surgery to obtain watertight closure.

Advances in surgical techniques and imaging technologies have allowed neurosurgeons to treat disorders of the spine that in prior decades were not amenable to surgical correction. Such disorders include intraspinal tumors, complicated spinal conditions such as Chiari malformations and congenitally acquired tethered cord syndrome, and other spinal disorders requiring instrumentation and/or fusion. In many cases, surgical treatment of these conditions requires incision of the dura mater. If the dural incision is not properly repaired and watertight closure is not achieved intra-operatively, cerebrospinal fluid (CSF) can escape from the subarachnoid spaces into the extradural compartment presenting a risk for significant morbidity. Achieving watertight closure intra-operatively is a basic objective of neurosurgical practice.

The intra-operative primary effectiveness endpoint was chosen for the Study after discussions with FDA and since it is consistent with previous studies on devices intended to seal. DuraSeal Cranial Sealant, CoSeal Surgical Sealant and BioGlue Surgical Adhesive are all FDA approved sealants studied in clinical trials using an intra-operative endpoint. The selection of an intra-operative endpoint in these studies is related to the realization that a leak-free primary repair at the time of the initial treatment is the primary goal of the surgical closure. There are many factors that are not procedure related, such as post-operative patient activity, which may lead to a post-operative CSF leak. For this reason and those stated above, the clinical Study was designed to provide data for the proposed indication; as an adjunct to sutured dural repair to provide intra-operative watertight closure during spinal surgery.

Surgeons do not have a safe and effective, FDA approved, adjunct to suturing for intra-operative watertight closure for spine surgery. They use a variety of approaches to ensure the surgical incision site does not leak spinal fluid. One method is to "oversew" the area, which means surgeons sew the stitches closer together in the tissues immediately overlying the surgical site. Some surgeons, after dural closure with sutures, pack the area with other tissues from the patient, such as fat, muscle, or connective tissue. If, following Valsalva maneuver, a leak persists, surgeons may use rescue therapy such as surgical hemostatic agents and fibrin glue to augment dural repairs. However, use of these materials in this manner constitutes an "off-label" use, as these products are not specifically indicated for dural repair. Fibrin glue and other animal or human derived products are commonly used as off label adjuncts to sutures. These materials are well-recognized by FDA to have unique risks of infection and immune reactions[1-4].

Citation 1. FDA Guidance for Industry. Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) – Small Entity Compliance Guide. August 2007.

Citation 2. FDA Guidance for FDA Reviews and Industry. Medical Devices Containing Materials Derived from Animal Sources (Except for In VitroDiagnostic Devices). November 16, 1998

Citation 3. FDA Guidance for the Preparation of a Premarket Notification Application for a Surgical Mesh. March 2, 1999.

Citation 4. FDA Guidance Document for Dura Substitute Devices; Guidance for Industry. November 9, 2000.

The use of the DuraSeal Spine sealant, a synthetic material, may reduce the risk of disease transmission or immune reaction.

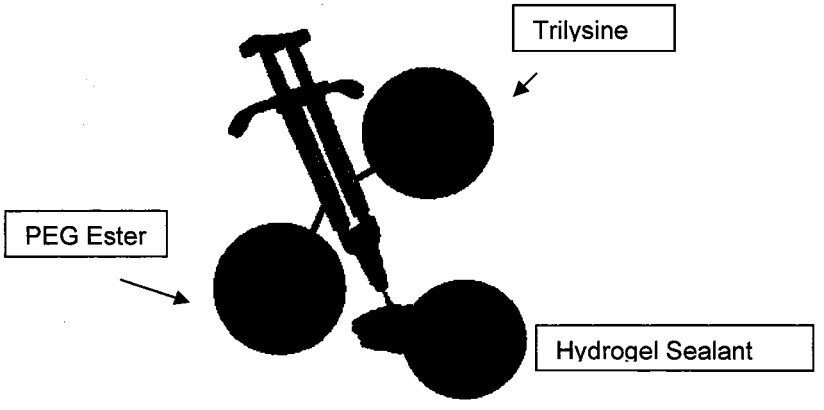
Surgeons and patients would benefit from an FDA approved intra-operative adjunct to sutures in spinal surgery. This adjunct is particularly needed for procedures where a CSF leak persists after the primary sutured closure. DuraSeal's 100% efficacy in this clinical Study precluded the need for additional animal or human derived products to achieve the primary endpoint of intra-operative watertight closure. In contrast, 33.9 % of subjects in the standard of care control arm required rescue therapy containing animal or human-derived materials, such as fibrin glue or DuraGen, to achieve a final watertight dural closure in the operating room.

1.2 DURASEAL SPINE SEALANT DEVICE DESCRIPTION

The DuraSeal Spine Sealant System consists of the components for preparation of a synthetic absorbable sealant, and applicators for delivery of the Sealant to the target site.

As shown in **Figure 1-1: DuraSeal Sealant**, the Sealant 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).

Figure 1-1: DuraSeal Sealant



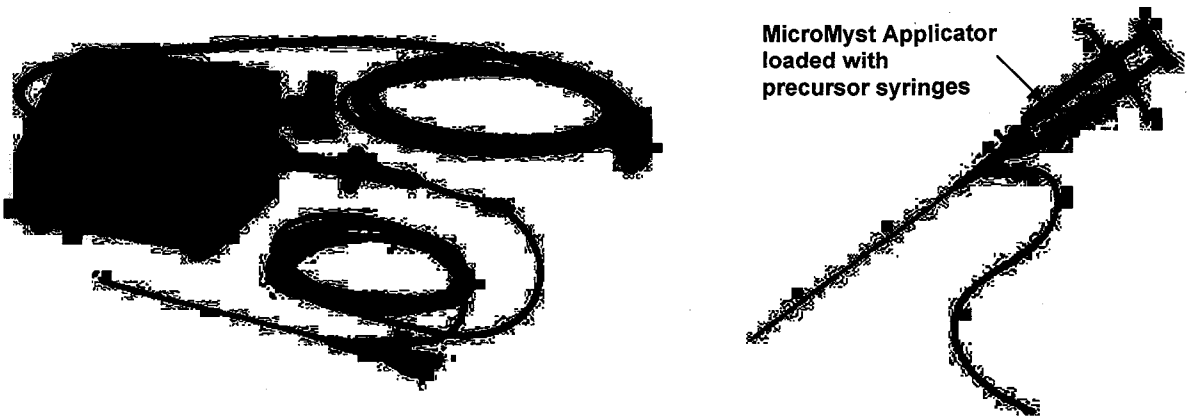
When mixed together, the precursors rapidly polymerize *in-situ* to form the hydrogel Sealant.

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 Spine Sealant can be used for up to one hour following reconstitution.

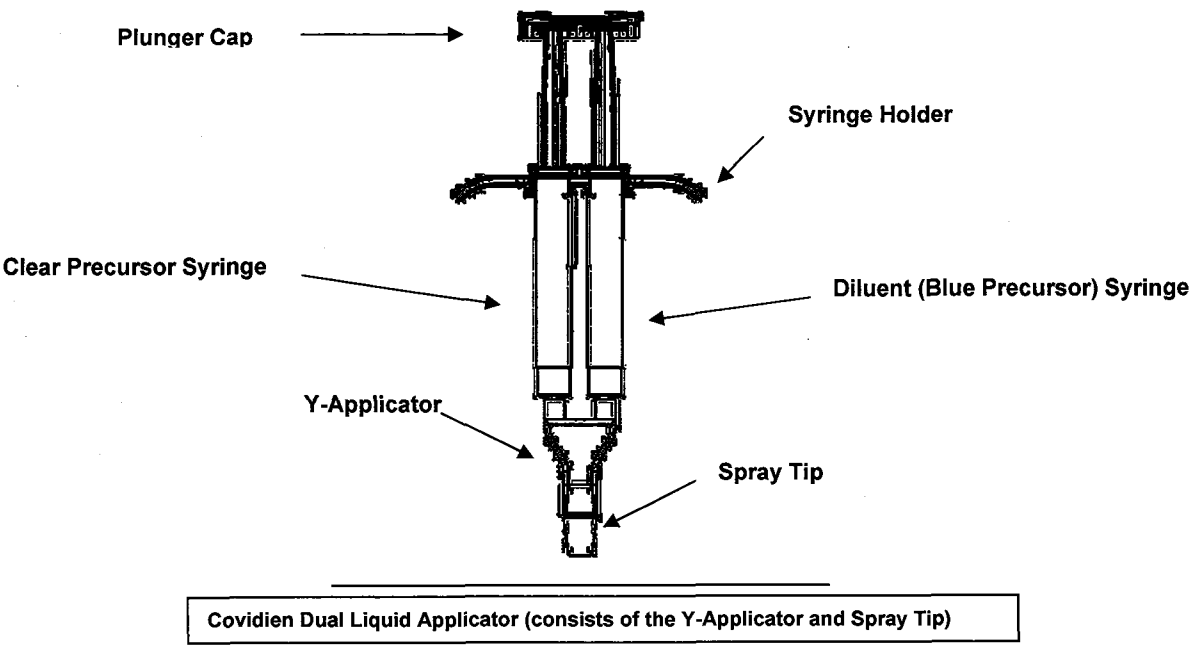
The DuraSeal Spine Sealant System is provided in two configurations. The 2 mL configuration consists of one 2 mL polymer kit packaged with one MicroMyst™ Applicator (the MicroMyst Applicator requires the use of a compressed air source, such as a Flow Regulator or Air Pump), refer to **Figure 1-2: Assembled DuraSeal Sealant System, 2-mL configuration**).

Figure 1-2: Assembled DuraSeal Sealant System, 2-mL configuration



The 5 mL configuration consists of a 5 mL polymer kit, which includes the Covidien Dual Liquid Applicator (consisting of the Y-Applicator and three (3) Spray Tips), refer to **Figure 1-3: Assembled DuraSeal Spine Sealant (5ml configuration)**.

Figure 1-3: Assembled DuraSeal Spine Sealant (5ml configuration)



1.3 DURASEAL SEALANT CLINICAL STUDIES

The clinical studies conducted to evaluate the Safety and Effectiveness of the DuraSeal Spine Sealant is summarized below in **Table 1-1: DuraSeal Sealant Clinical Studies**

Table 1-1: DuraSeal Sealant Clinical Studies

Study	Study Design	Results (Primary Endpoint)
DuraSeal European Pilot Study (Cranial and Spine)	A prospective, single center, non-randomized clinical investigation to evaluate the safety and performance of the dural Sealant in patients scheduled for elective cranial or spinal surgery was performed between February 20 and September 23, 2002 by J. Andre Grotenhuis, MD, PhD, at the Neurosurgery Center, Nijmegen, and The Netherlands. A total of 47 patients were treated with the dural sealant: 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 dural Sealant demonstrated a CSF leak during the post application Valsalva maneuver, thus demonstrating a 100% success rate in holding a intra-operative watertight seal
DuraSeal Multi-Center US Pivotal Study (Cranial Study)	A prospective, multi-center, non-randomized, single arm clinical investigation to evaluate the safety and effectiveness of the dural Sealant as an adjunct to sutured dural repair during cranial surgery was conducted. The Study involved 10 investigational sites within the United States and 1 site in Europe. A total of 111 patients were treated with the dural sealant.	All 111 patients treated with the dural Sealant showed no leakage during the intra-operative assessment. 109 of 111 patients (98.2%) met the criteria for primary endpoint success; i.e., intraoperative sealing. Two patients were tested intra-operatively at a pressure of only 10 cm H_2O, and although no leak was seen, these patients could not technically be classified as successes.

Study	Study Design	Results (Primary Endpoint)
DuraSeal Multi-center, randomized, two arm, single blind Study (Spinal Study)	This was a prospective, multi-center, randomized, two arm, single blind Study designed to assess if the DuraSeal Spinal Sealant System, when used as an adjunct to sutured dural repair, is more effective than Standard of Care methods for producing a watertight dural closure in subjects undergoing an intentional durotomy during spinal surgery. One hundred and two (102) patients were treated with the DuraSeal Spine Sealant System and 56 patients were treated using Standard of Care (Control) methods.	All 102 subjects (100%) treated with the hydrogel Sealant met the criteria for primary endpoint success, i.e. intra-operative sealing. 36 of the 56 subjects (64.3%) treated with Standard of Care methods displayed a watertight closure after assigned treatment.

1.4 SUMMARY OF DURASEAL SPINE PIVOTAL STUDY RESULTS

The DuraSeal Spine Pivotal Study was designed as a prospective, multi-Center, randomized controlled Study. It was designed to provide data for the proposed indication; as an adjunct to sutured dural repair to provide watertight closure during spinal surgery. One hundred and two (102) subjects were treated with the DuraSeal Spine Sealant System and 56 subjects were treated using Standard of Care (Control) methods. The main pre-operative criteria for Study inclusion were subjects who were between 18 and 75 years old, were undergoing a spinal procedure that requires an intentional dural incision, and provided informed consent on an IRB-approved consent form. Intra-operatively, the main criterion for randomization was presence of a non-watertight dural closure, e.g., persistent leak, after attempted standard closure with sutures.

The control arm received the investigator's standard of care control method for sealing intra-operatively. Dural replacement/grafts, such as commercially available DuraGen® Dural Graft Matrix, were not permitted as a Control method, as the device is designed as a duraplasty material, not as a sealant. Hemostatic agents, such as commercially available Gelfoam®, were not permitted as a Control method, as this device is designed to pack the wound and not as a sealant.

The additional parameter set around the rescue therapy, after primary endpoint evaluation, permitted by the Study protocol was identified by FDA in the IDE conditional approval letter. FDA indicated, "Surgeons may opt to add additional devices that are not designed to provide an intraoperative watertight closure (such a Gel-foam or Duragen) after the Valsalva maneuver is completed".

Intraoperative Procedures (Per Study Protocol):

Application of the "Standard of Care" (Control Method)

After primary dural closure, if a Study subject was randomized to the control arm, the Investigator would choose their standard of care method (i.e., devices designed to provide an intraoperative watertight closure). In most cases, this included either adding additional sutures or applying adhesive glue, or a combination of the two methods. The investigator could make up to two attempts with the chosen Control method, to achieve a watertight closure evidenced by a Valsalva maneuver. The choice whether a second attempt was necessary was at the discretion of the investigator and was not mandatory per the Study protocol. If the investigator chose to make a second attempt, they were required by the Study protocol to be consistent in using the same Control technique they chose for their first attempt.

Rescue Therapy

If the investigator was not able to obtain a watertight dural closure after up to two attempts n either treatment arm (DuraSeal Spinal Sealant or Control), the subject was deemed to be a primary endpoint failure. Since intraoperative dural closure is a basic tenant of neurosurgery, the Investigator was then permitted to use any further "rescue" materials/methods of their choosing to achieve a watertight closure of the dura, including DuraGen®, Tisseel®, and Gel-foam. The rescue therapy was completed per the investigators standard procedure. Note that the use of DuraSeal (Spine or Cranial) was not permitted in the Control arm at any time.

Efficacy results:
Of the 158 subjects randomized, all 102 subjects (100.0%) treated with the DuraSeal DuraSeal Spinal Sealant and 36 of the 56 subjects (64.3%) treated with Control methods displayed a watertight closure after assigned treatment. Three (3) subjects randomized to Control were considered not evaluable for the per protocol analysis of the primary efficacy endpoint, as the investigator chose not to use any of the Control methods per the protocol (i.e., devices designed to provide an intra-operative watertight closure).

Intent to Treat Population (n = 158):
DuraSeal Spinal Sealant = 102 successes (100%)
Standard of Care = 36 successes (64.3%)

Per Protocol Population (n = 155):
DuraSeal Spinal Sealant = 102 successes (100%)
Standard of Care = 36 successes (67.9%)

For both the Intent to Treat and Per Protocol analyses, the difference in primary endpoint success rates was highly significant with a p-value <0.001. Three subjects in the Control arm had an intra-operative leak, but the surgeons felt that the predefined, per protocol treatments were not appropriate. If we impute a successful outcome for these three subjects, the difference is still statistically significant at less than 0.001; therefore, success criterion for the Study has been satisfied and the data demonstrate that the DuraSeal Spinal Sealant is superior to the Standard of Care employed within the Control arm for providing an intraoperative watertight closure following sutured dural repair.

Safety results:
For those control subjects that failed the primary effectiveness endpoint, rescue methods were used by the surgeon to ensure a watertight intra-operative seal. Rescue methods reinforced the dura with material such as synthetic duraplasty materials (i.e., dural graft matrix) or direct dural overlay of an absorbable sponge. Within the DuraSeal Spinal Sealant arm, dural repair was limited to sutures and sealant. Therefore, all control Safety Assessments are based on complete intra-operative sealing regardless of primary endpoint outcome.

The incidence of protocol defined post-operative CSF leaks was comparable between the two treatment arms; DuraSeal Spinal Sealant 7.8% vs. Control 5.4% (p= .748) and the time to CSF leak onset (p=0.578, log rank test) was also comparable.

The rate of adverse events in the Study demonstrated that the DuraSeal Spine arm had statistically higher events in the Injury, Poisoning And Procedural Complications and Renal/Urinary System Organ Class for this population tested, most resolved without complication. Possible explanations for the differences include:

1. The Study was not powered given the incidence rates of adverse events observed.

2. The 2:1 randomization of the Study increased the chance of more adverse events being shown in the Sealant arm.

3. A potential reporting bias since the investigator and the CEC committee were unblinded.

The incidence of surgical site infections was also comparable between the two arms; DuraSeal Spinal Sealant 6.9% vs. Control 7.1% (p=1.000).

The overall event profile for subjects treated with the DuraSeal Spinal Sealant was similar to that of the Control arm within the majority of System Organ Classes (SOCs) and consistent in nature for this Study population, a population undergoing neurosurgical procedures. There were no clinically relevant differences in safety outcomes between the two treatment arms with respect to laboratory evaluations, neurological exams, vital signs, physical examination and wound healing.

The DuraSeal Spinal Sealant Study and the DuraSeal Cranial Post Approval Study[2] captured events related to the neurological procedures. Fourteen categories of complications are collected in the DuraSeal Cranial Study, among them Surgical Site Infections, CSF Leaks, Hydrocephalus, Cerebral Hemorrhage and Cerebral Edema. Interim data for three classes of surgical site infections (per CDC guidelines) and post-operative CSF leaks are presented as they are relevant to spinal procedures and were reported using the same criteria as the DuraSeal Spinal Sealant Study.

The DuraSeal Cranial Post Approval Study captured infections based on the CDC Guidelines for classification of surgical site infections. Of the 118 DuraSeal randomized subjects, 2/118 (1.7%) had a superficial surgical site infection, 1/118 (0.8%) had an organ/space surgical site infection, and 0 (0.0%) encountered a deep surgical site infection. In the control arm, 4/115 (3.5%) experienced a superficial surgical site infection and none experienced an organ/space or deep surgical site infection.

The defined criteria for Post-Operative CSF leak was clearly outlined in the DuraSeal Spinal Sealant Study and the DuraSeal Cranial Post Approval Study protocol. For both studies, determination of a post-operative CSF leak (occurring within 30 days in the DuraSeal Cranial Study) was by one of the following three methods: CSF leak or pseudomeningocele related surgical intervention, CSF leak confirmation by diagnostic testing, or CSF leak determination by clinical evaluation. Of the 118 DuraSeal randomized subjects in the DuraSeal Cranial Post Approval Study, 1/118 (0.8%) had a protocol-defined post-operative CSF leak. Of the 115 control subjects, 3/115 (2.6%) had a protocol-defined post-operative CSF leak.

This data indicates that when a larger population is tested, e.g., DuraSeal Cranial Post Approval Study, the adverse event rates for infection and CSF leak are similar between the two arms, DuraSeal Spinal Sealant and surgeon standard of care control method.

In addition, the DuraSeal Dural Sealant System has also been marketed in a 5ml kit outside the United States since 2003; indicated as an adjunct to standard methods of dural repair to provide watertight closure in cranial and spine procedures and; marketed in a 2ml kit outside of the United States since 2005; indicated as an adjunct to standard methods of dural repair, such as sutures, to provide watertight closure during spine procedures.

Based on the ex-US spinal/cranial Sealant approvals, there is a significant amount of experience with the device. As of March 2009, there have been 43,854 units sold. Based on these sales, there have been 31 are Medical Device Reportable complaints (0.07%); 21/31 are coded as infection (0.05%), 9/31 CSF Leak/Pseudomeningocele (0.02%), and 1/31(0.01%) as medical complication. Covidien takes a conservative approach on MDR reporting and any reports that cannot be definitively assessed as device related are MDR reported.

In summary, the DuraSeal Spinal Sealant Study results and the significant amount of experience with the device demonstrate the DuraSeal Spinal Sealant is safe. To confirm the adverse event profile of the DuraSeal Spine Sealant the sponsor will perform a post-approval Study in a larger patient population. This Study will further confirm adverse event rates associated with use of the DuraSeal Sealant versus surgeon standard of care.

[2] The DuraSeal Cranial Study is not complete and therefore, the data has not been fully audited.

1.5 INDICATIONS FOR USE

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

1.6 CONTRAINDICATIONS

The DuraSeal Spine 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.

1.7 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.

1.8 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 as a 5ml kit outside the United States since 2003 as an adjunct to standard methods of dural repair to provide watertight closure in cranial and spine procedures and; marketed as a 2ml kit 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.

Based on the ex-US spinal/cranial Sealant approvals, there has been a significant amount of experience with the device. There have been [redacted] units sold as of March 2009.

2.0 DURASEAL SPINE SEALANT IN VITRO, IN VIVO, AND CLINICAL STUDIES

2.1 IN VITRO PRODUCT TESTING

A series of *in vitro* tests were performed to evaluate the PEG material and the components of the DuraSeal Spine Sealant System (final, sterilized devices). The results are summarized in **Table 2-1: In Vitro Product Testing** below.

Table 2-1: 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 Spine Sealant 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.
Biocompatibility	ISO 10993	The DuraSeal Spine Sealant meets the requirements of ISO 10993.

2.1 IN VIVO (ANIMAL TESTING)

A series of animal studies were conducted to evaluate the *in vivo* performance and safety of the DuraSeal Spine Sealant System. **Table 2-2: Summary of Animal Studies** provides a summary of the tests performed and the relevant findings.

Table 2-2: 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	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. 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 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-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.
Hydrogel Appearance under MR and CT Imaging	2 test (hydrogel)/14 weeks	Histopathology showed minimal changes, with excellent tissue compatibility of the hydrogel. Histological examination found an unremarkable response with no neurotoxicity, or space-filling defect. 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.
Implantation of Hydrogel in Rat Brain Parenchyma	8 test (hydrogel) and 8 control/42 days	No neurologic deficits were noted and no adverse reactions were observed for any of the test sites at explant. 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 arm were euthanized.
Neurotoxicity Study in the Rat Following Injection into the Brain	13 test (hydrogel) and 13 control/2 weeks	The microscopic evaluation of the tissues revealed no evidence of a treatment related response. 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 arm were euthanized and necropsy performed. No macroscopic encapsulation was observed at any test or control cannulation site.
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. 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.
Study for Effects on Embryo-Fetal Development in Rats Following Intraperitoneal Administration	25 test (hydrogel) and 25 control/2 weeks	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. 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.
Canine Lumbar Laminectomy Study	13 animals, two surgical sites per animal: treatment (hydrogel) or surgical control (no treatment)/12 - 14 weeks	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. 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 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

Test Performed	# Animals/ Study Duration	Summary/Relevant Findings
		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.	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. 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.

2.2 CLINICAL STUDIES

2.2.1 European Pilot Study

A prospective, single center, non-randomized clinical investigation to evaluate the safety and performance of the dural Sealant in patients scheduled for elective cranial or spinal surgery was performed between February 20 and September 23, 2002 by J. Andre Grotenhuis, MD, PhD, at the Neurosurgery Center, Nijmegen, The Netherlands. A total of 47 patients were treated with the dural sealant: 45 (95.7%) cranial and 2 (4.3%) spinal intra-dural procedures.

The sutured dural repair was completed to the investigator's satisfaction; autologous duraplasty materials to aid in the sutured closure (i.e. fascia, fat, pericranium, or muscle) were used as necessary. Upon completion of the sutured dural repair, the closure was evaluated for cerebrospinal fluid (CSF) leakage with a baseline Valsalva maneuver to 20 cm H_2O. If a spontaneous leak was already apparent immediately after dural closure, no Valsalva was performed.

If a leak was present, either spontaneously or upon Valsalva, and the patient was found to be eligible per the intra-operative criteria, the dural Sealant was applied to the closure site and a subsequent Valsalva maneuver was conducted to evaluate the ability of the device to hold a watertight seal.

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 dural Sealant demonstrated a CSF leak during the post application Valsalva maneuver, thus demonstrating a 100% success rate in holding a watertight seal. There were two cases of overt CSF leaks (4.7%) and one case of pseudomeningocele (2.3%), all of which had a surgical intervention within the one-month post-operative period.

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 SAE's in 11 patients or an overall incidence of 29.8% SAE's in the Study. None of the reported adverse events were related to the dural sealant.

The clinical Study demonstrated the safety and performance of the dural Sealant for its intended use as an adjunct to standard methods of dural repair, such as sutures, to provide watertight closure for the reduction of CSF leaks intra-operatively.

2.2.2 DuraSeal Cranial Pivotal Study[3]:

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

One hundred five (105) patients (94.6%) were treated with one dural sealant application, and 6 patients (5.4%) were treated with two applications.

All 111 patients treated with the dural sealant showed no leakage during the intra-operative assessment. 109 of 111 patients (98.2%) met the criteria for primary endpoint success; i.e., intra-operative sealing. Two patients were tested intra-operatively at a pressure of only 10 cm H_2O, and although no leak was seen, these patients could not technically be classified as successes.

Safety was assessed based on evaluation of wound healing, the occurrence of post-operative CSF leaks and the nature and severity of other adverse events. Subjects were evaluated at discharge, at six weeks and three months post-procedure. One hundred (100) patients (90%) were noted to have experienced at least one event with a total of 444 events. The majority (88%) of these adverse events were non-serious. Thirty-two (32) patients (29%) experienced a total of 54 serious adverse events. There were no unanticipated adverse device effects.

A visual wound healing assessment was performed at each post-operative visit. At the 3-month assessment, all 107 patients (100%) that continued in the study were well healed. For the majority of patients (81%), all swelling had resolved by the 6 week visit. Eight (8) patients (7.2%) exhibited persistent swelling at the 3-month visit and of these six (6) were limited to localized swelling at the incision.

Eight (8) of 111 subjects (7.2%) experienced a deep surgical site infection, while one (1) subject (0.9%) experienced a superficial surgical site infection and one (1) subject (0.9%) was noted to have a hematoma.

Protocol defined post-operative CSF leaks (including both incisional leaks and pseudomeningoceles requiring surgical intervention) occurred in 4.5% patients (5/111) and were absent for 106 patients (95.5%, 95% C.I: 89.8-98.5). For the five (5) patients with endpoint CSF leakage, the time to first endpoint CSF leakage ranged from 7 to 29 days. Two of the five (2/5) CSF leak events presented as incisional CSF leaks and three (3) events presented as pseudomeningoceles.

[3] The data gathered under this clinical investigation were previously submitted to and reviewed by FDA as part of PMA P040034 for the DuraSeal Dural SealantSystem.

2.3 DURASEAL SPINE PIVOTAL STUDY (DRS 05-001)

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.

Since neurosurgeons use several different types of products that are not designed to provide a watertight dural closure (and thus would constitute off-label use e.g., duraplasty, hemostatic agents), an additional parameter was placed around the "Standard of Care". The Study protocol dictated that while "Standard of Care" methods were to be employed for Control subjects, the devices chosen must be those that were designed to provide a watertight closure, "Patients that are randomized to the control arm may be treated with up to two treatments with the chosen standard of care method (i.e., devices that are designed to provide an intraoperative watertight closure)." This additional parameter also ensured that the investigator would use Control devices that allowed him/her to adequately visualize and confirm the primary endpoint outcome with a Valsalva maneuver. With this additional parameter around the "Standard of Care" in place, the Control treatment chosen by a majority of Study investigators was either the application of additional sutures or adhesive glue (Fibrin Glue). Fibrin Glue is FDA-approved for use as a hemostatic agent in cardiopulmonary bypass and splenic injury procedures, but is commonly used off-label by neurosurgeons for purposes of spinal dural sealing. While the safety and efficacy of Fibrin Glue for this indication has not been proven in a randomized controlled clinical Study, the device is designed to seal by means of providing a mechanical barrier over the leaking area.

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 Sealantor 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.

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 Sealantor 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 Sealantor 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 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 2-3: Subject Demographics.**

Table 2-3: 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)
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 2-4: Location of Procedure.**

Table 2-4: Location of Procedure

Cervial	46	57
Thoracic	38	27
Lumbar	25	27
Sacral	9	2

2.3.1 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; therefore, the success criterion for the Study has been satisfied.

We performed additional post hoc statistical analysis of effectiveness results. Following the definition of the Study protocol, the surgeon was required to use the same Control Method for both attempts in achieving a watertight closure. In 4 subjects the surgeon's chosen control method was not fibrin glue. It was decided after the first Control attempt had failed that a second attempt was not appropriate. Rescue therapy was then applied to the dura. Per the Study protocol, these cases were coded as failures. However, since the rescue therapy chosen was Fibrin Glue, a Control treatment permitted by the protocol for first or if required, second attempt, a post hoc statistical analysis was performed, imputing a successful outcome in these four subjects, **Table 2-5: Sensitivity Analysis (Effectiveness)**.

Table 2-5: Sensitivity Analysis (Effectiveness)

Overall	n/N (%)	102/102(100.0)	40/56(71.4)	28.6
	95% CI for %	(96.4,100.0)	(57.8, 82.7)	(16.7, 40.4)
	p-value (1)	<0.001		

In addition to the 4 subjects above, 13 other subjects were declared primary endpoint failures without receiving two attempts of control. Below **Table 2-6: Post Hoc Analysis (17 subjects)** imputing a successful outcome in these seventeen subjects.

Table 2-6: Post Hoc Analysis (17 subjects)

Overall	n/N (%)	102/102(100.0)	53/56(94.6)	5.4
	95% CI for %	(96.4,100.0)	(85.1, 98.9)	(0.0, 11.3)
	p-value (1)	0.043		

The results of these sensitivity analyses indicate that the primary effectiveness endpoint was still met with statistical significance.

2.3.2 Safety Evaluations

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 unblended 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 2-7: Incidence of Protocol Defined Post-Operative CSF Leaks**. This difference is not statistically significant, p=0.748, two sided Fisher Exact test.

Table 2-7: Incidence of Protocol Defined Post-Operative CSF Leaks

Category	Statistic	DuraSeal Spinal Sealant (N=102)	Control (N=56)	Difference (%)	p-value (1)	95% C.I. of Difference (%)
Presence of endpoint CSF leak within 90 days post-procedure	n (%)	8 (7.8)	3 (5.4)	2.5	0.748	-5.4, 10.4
CSF Fistula	n	3 (2.9)	0	2.9	0.553	-0.3, 6.2
Pseudomeningocele	n	5 (4.9)	3 (5.4)	0.5	1.000	-7.7, 6.8

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(1) p-value is based on two-sided Fisher's Exact test testing for a difference between treatments.

As detailed above, the rates of postoperative CSF leaks that manifested as a pseudomeningocele was similar among arms with the Control arm experiencing a slightly higher percentage. As there were differences in the percentages among CSF fistula a brief summary is provided below.

[redacted] underwent a spinal cord de-tethering in the L5-S1 region. During suture removal, approximately 13 days post-op, a small wound separation occurred and a small amount of CSF leaked from the wound. Due to the risk of possible meningitis the subject underwent wound exploration. Intra-operative exploration revealed CSF leakage through a

small fascial defect. The fluid was never tested to confirm CSF. The CEC was unable to determine the relatedness of the event, as the subject experienced severe post-op nausea and vomiting and there was no exploration deeper than the fascia and the Sealant was never inspected during the re-operation.

[redacted]underwent surgery for a Chiari Malformation with cervical syringomyelia. The subject developed a CSF leak 22 days post-op, while bike riding. The leak was initially treated conservatively with over-sewing, but persistent leakage prompted surgical intervention. They were taken back to the operating room for dural repair. The CEC adjudicated this event as related to the surgical procedure.

[redacted]underwent surgery for syringomyelia at the C5 level. Of note, this subject should not have been enrolled in the Study as they exhibited several pre-operative and intra-operative exclusion criteria including previous spinal surgery and required for use of a non-autologous duraplasty material for primary closure. The surgeon commented that the dissection and laminectomy took approximately 3 hours since there was a significant amount of scar tissue and calcification. It was also noted that there was no dura at the C5 level and there was a "struggle" to close the dura due to the poor quality. Eight days post-op, the subject experienced clear drainage to the neck dressing, they were admitted and a lumbar drain was placed. The CEC adjudicated the event as related to the procedure.

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: 2-8:Endpoint CSF Leakage (Safety Population)**.

Table: 2-8:Endpoint CSF Leakage (Safety Population)[4]

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		

[4] The DuraSeal Spine SealantClinical Study Report DRS-05-001 included a [redacted] with onset of a post-op leak at 70 days. This was reported in error. The onset of the leak was at 29 days.

In this analysis presented 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 infections 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 exact test, **Table 2-9: Incidence of Surgical Site Infections.**

Table 2-9: Incidence of Surgical Site Infections

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Presence of SSI within 90 days post-procedure	7 (6.9)	4 (7.1)	-0.2	1.000	-8.6, 8.1
Deep Surgical Site Infection	5 (4.9)	1(1.7)	-3.2	0.424	-2.3, 8.6
Superficial Surgical Site Infection	2(2.0)	3(5.4)	3.4	0.667	-9.2, 4.3

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(1) p-value is based on two-sided Fisher's Exact Test testing for a difference between treatments.

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 which occurred within the DuraSeal Spinal Sealant arm. There were five subjects who developed a deep surgical site infection in the Spine 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 MRSA which is a finding consistent with hospital acquired infections. All but one event [redacted] resolved without sequelae by the 90 post-operative visit. [redacted], 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 [redacted]

ADVERSE EVENTS, SERIOUS ADVERSE EVENTS AND DEVICE RELATED ADVERSE EVENTS

Serious adverse events (SAEs) and device-related adverse events were also examined separately. Please refer to Clinical Protocol for a description of the safety statistical analysis.

Adverse Event Overview

Table 2-10: 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 2-10: Summary of Adverse Events (AEs) and Serious Adverse Events (SAEs)

Category	DuraSeal Spinal Sealant (N=102) n (%)	Control (N=56) n (%)	p-value (1)
Number of Subjects (%) With At Least One AE	95 (93.1)	51 (91.1)	0.639
Number of Subjects (%) With At Least One SAE	30 (29.4)	10 (17.9)	0.110

Program Name: D:\CONFLUENT\DRS-05-001\INTEXTAB\T14.SAS Creation Date, Time: 09APR08 17:12
(1) p-value from Pearson's chi-square test or Fisher's exact test for a difference between treatment arms in the percentages of patients experiencing at least one AE in that given category as appropriate.

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 2-11: 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, [redacted] 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 2-11: 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)

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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 2-12: Adverse Events by System Organ Class (Safety Population) presents the incidence of adverse events within each System Organ Class.

Table 2-12: Adverse Events by System Organ Class (Safety Population)

System Organ Class	DuraSeal Spinal Sealant (N=425), %	Control (N=165), %	p-value (%)	95% C.I. of Difference (%)
Blood And Lymphatic System Disorders	10 (9.8)	4 (7.1)	0.772	(-6.2, 11.5)
Cardiac Disorders	10 (9.8)	2 (3.6)	0.216	(-1.3, 13.8)
Eye Disorders	6 (5.9)	1 (1.8)	0.423	(-1.6, 9.8)
Gastrointestinal Disorders	21 (20.6)	9 (16.1)	0.532	(-7.9, 16.9)
General Disorders And Administration Site Conditions	33 (32.4)	18 (32.1)	1.000	(-15.0, 15.4)
Immune System Disorders	1 (1.0)	0 (0.0)	1.000	(-0.9, 2.9)

Infections And Infestations	19 (18.6)	9 (16.1)	0.828	(-9.7, 14.8)
Injury, Poisoning And Procedural Complications	44 (43.1)	7 (12.5)	<0.001	(17.7, 43.6)
Investigations	50 (49.0)	23 (41.1)	0.405	(-8.2, 24.1)
Metabolism And Nutrition Disorders	10 (9.8)	3 (5.4)	0.384	(-3.8, 12.7)
Musculoskeletal And Connective Tissue Disorders	24 (23.5)	15 (26.8)	0.701	(-17.5, 11.0)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	4 (3.9)	0 (0.0)	0.298	(0.2, 7.7)
Nervous System Disorders	48 (47.1)	21 (37.5)	0.315	(-6.4, 25.5)
Psychiatric Disorders	4 (3.9)	3 (5.4)	0.699	(-8.4, 5.6)
Renal And Urinary Disorders	20 (19.6)	4 (7.1)	0.039	(2.2, 22.7)
Reproductive System And Breast Disorders	1 (1.0)	1(1.8)	1.000	(-4.8, 3.2)
Respiratory, Thoracic And Mediastinal Disorders	15 (14.7)	4 (7.1)	0.206	(-2.1, 17.2)
Skin And Subcutaneous Tissue Disorders	9 (8.8)	3 (5.4)	0.541	(-4.6, 11.5)
Vascular Disorders	10 (9.8)	6 (10.7)	1.000	(-10.9, 9.0)

Program Name: D:\CONFLUENT\DRS-05-001\INTEXTAB\T16.SAS Creation Date, Time: 15APR08 09:26
(1) p-value from Fisher's exact test for a difference between treatment arms in the percentages of patients experiencing at least one AE in that given system organ class.
(2) 95% CI for the difference was calculated based on normal approximation
Note: Percentages may total more than 100%.

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 [redacted] 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. 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, despite multiple testing, **Table 2-13: Serious Adverse Events Presented by SOC and Preferred Term.**

Table 2-13: Serious Adverse Events Presented by SOC and Preferred Term

System Organ Class Preferred Term	DuraSeal Spinal Sealant (N=102)	Control (N=56)	p-Value
Any Serious Adverse Event	30 (29.4)	10 (17.9)	0.128
Gastrointestinal Disorders	3 (2.9)	2 (3.6)	1.000
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)	1.000
Pyrexia	1 (1.0)	0 (0.0)	
Infections And Infestations	1 (1.0)	2 (3.6)	0.287
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)	0.073
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)	1.000
Mobility Decreased	1 (1.0)	0 (0.0)	
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	1 (1.0)	0 (0.0)	1.000
Brain Cancer Metastatic	1 (1.0)	0 (0.0)	
Nervous System Disorders	9 (8.8)	1 (1.8)	0.099

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)	0.615
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)	1.000
Pulmonary Embolism	1 (1.0)	2 (3.6)	
Respiratory Failure	2 (2.0)	0 (0.0)	
Vascular Disorders	1 (1.0)	1 (1.8)	1.000
Deep Vein Thrombosis	1 (1.0)	1 (1.8)	

Program Name: D:\CONFLUENT\DRS-05-001\INTEXTAB\T17.SAS Creation Date, Time: 09APR08 17:18
(1) p-value from Fisher's exact test for a difference between treatment arms in the percentages of patients experiencing at least one AE in that given system organ class.
(2) MedDRA preferred terms including events of deep SSI
(3) MedDRA preferred terms including events of endpoint CSF leaks

NERVOUS SYSTEM DISORDERS

As previously discussed, there was a statistical difference between the DuraSeal Spinal Sealant and the Control arms for "Renal and Urinary Disorders" (19.6% vs. 7.1% respectively; p=0.039) and "Injury, Poisoning and Procedural Complications" (43.1% vs. 12.5%; p<0.001). Although not statistically significant, there were 9 DuraSeal Spinal Sealant subjects and 1 control subject that had events classified as SAE under the Nervous System Disorder SOC. None of these events were attributed to the use of the device. Instead, they were related either to the procedure or the subject's underlying condition.

The following subjects experienced a major neurological deficit post-operatively and are discussed in greater detail:

[redacted] underwent removal of a conus medularis tumor from the T12-L1 region. 2.0 mL of DuraSeal Spinal Sealant were applied to a 10.5 cm durotomy. During post-op day 1, the subject was noted to have ataxic gate when out of bed and required the use of a walker due to lower extremity weakness and numbness. The subject's hospital stay was extended to a total of 8 days for continued therapies to increase mobility and independence. The event was still ongoing at the 90-day follow-up visit, but had improved significantly.

The CEC determined that this event was related to the patient's prior condition.

[redacted] underwent partial removal of a T3-T4 malignant meningioma. During the procedure, it was determined that the tumor was malignant and most likely metastasis versus a primary hemopoietic type tumor, and as a result a more aggressive resection was not deemed appropriate.
The subject had strength in the bilateral lower extremities at baseline which quickly deteriorated post surgery. The day following surgery, the subject complained of bilateral lower extremity and tingling, an MRI showed increased spinal cord edema. Over the next day, the subject gradually became hemiplegic with mild sensory changes in their upper extremity. A small hematoma and signal abnormality was seen on MRI. The subject's sensory and motor functions deteriorated quickly over the course of the next several days and at approximately 5 days post-op, the subject reported no sensation below the nipple line. They were taken back to the operating room for surgical site exploration, decompression at two levels above the site, and evacuation of the hematoma. The surgeon noted the tumor seemed to be the source of the hematoma. Following the second surgical procedure, the subject's paralysis did not worsen, but did not improve. At the 90-day visit, the subject continued to report no sensation in the bilateral lower extremities and decreased sensory function below T7.

The CEC adjudicated both the subdural hematoma and paralysis as not related to the Study device, but to the surgical procedure.

[redacted] removal of spinal tumor at the C4-C7 region. Pathology revealed the intramedullary tumor as ependymoma, anaplastic, tanycytic (WHO grade III).
One day after surgery, the subject was noted to have sensory ataxia and incomplete paraplegia. It is important to note that the subject had pre-existing neurological deficits at baseline, specifically bilateral lower extremity weakness and numbness in the upper left and lower right extremities.

They were transferred to a rehabilitation facility, and remained until 3 weeks post-op. At the 30-day follow-up visit, they were noted to be making reasonable progress with regards to strength, balance and dexterity. MRI revealed fairly significant edema with residual tumor.
The subject did return for the end of Study visit until almost 6 months post-op. At this time, they were ambulating with a cane and left leg brace.

The CEC determined that this event was not related to the device, but was being attributed to the subject's pre-existing deficits exacerbated by the procedure.

[redacted] removal of an intramedullary spinal cord tumor, probably hemangioblastoma at the T1-T2-T3 levels. On the same day of surgery, the subject developed bilateral lower extremity numbness and right lower extremity weakness. This was a worsening of a pre-existing condition, as the subject had right lower extremity weakness and reduced sensation in the bilateral lower extremities at baseline. At the subject's 90-day follow-up visit, they were able to ambulate with the assistance of a walker.

The CEC determined that this event was not related to the device, but to the procedure.

RELATIONSHIP OF ADVERSE EVENTS TO STUDY TREATMENT

For each reported adverse event, the investigator was required to determine if there was a causal relationship between the Study treatment and the event. Causality could be rated as "Yes", "No" and "Unable to Determine". If the investigator chose "No", a further classification was required, specifically "Procedure", "Patient's Prior Condition", "Concomitant Medication", or "Other – specify".
No adverse events were determined to be treatment (DuraSeal Spinal Sealant or Control) related, with the exception of one. [redacted] experienced a pseudomeningocele that required a surgical repair and was deemed to be related to the DuraSeal Spinal Sealant , per the Investigator. The CEC reviewed all source documents and deemed the event was related to the procedure and the subject's prior medical condition, rather than the DuraSeal Spinal Sealant .

As noted previously, in the majority of cases, the CEC agreed with the Investigator's assessment of relationship of the event to the assigned treatment. In twenty (20) instances there were differences in their assessments. In most of these instances (18 of 20) the Investigator deemed the relatedness as "Unable to Determine" and the CEC deemed it was "Not Related". In 6 cases the investigator deemed the relatedness as "Not Related" while the CEC was unable to determine the relationship.

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. As noted in **Table 2-12: Adverse Events by System Organ Class (Safety Population)** and **Table 2-13:**

Serious Adverse Events Presented by SOC and Preferred Term, 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, HCT, HgB, Platelet count), Electrolytes (Na, K, Cl, CO_2), Renal Function (BUN, Creatinine), Liver Function (alkaline phosphatase, Total Bilirubin, ALT, 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 [redacted] 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 thorough review of subject medical records. The CEC's overall impression was that, within each treatment arm, the observed events appeared consistent in type and severity for the Study population. At no time during the course of the Study were any recommendations made by the CEC that either the device or investigational plan be modified.

OTHER DATA ANALAYSIS

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 QUESTIONNAIRE

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.

SAFETY 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 closer.

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, possible explanations for the differences include:

4. The Study was not powered given the incidence rates of the serious adverse events observed.

5. The 2:1 randomization of the Study increased the chance of more adverse events being shown in the Sealant arm.

6. A potential reported bias since the investigator and the CEC committee were unblinded.

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.

OVERALL CONCLUSIONS

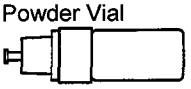
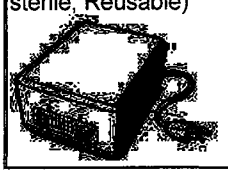
Based on the data presented, the Spinal Sealant System has been established to be safe and effective for providing a watertight closure when used as an adjunct to suture dural repair during spinal surgery. This Spinal Sealant will provide neurosurgeons with a readily available tool for constructing watertight 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 suture dural repair during spine surgery.

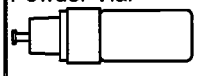
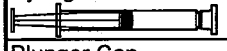
3.0 CHARACTERISTICS OF THE 2ML AND 5ML DURASEAL SPINE SEALANT KITS

3.1 DURASEAL SPINAL SEALANT SYSTEM COMPONENTS

Table 3-1: DuraSeal Spine Sealant System Components provides an overview of the physical characteristics in the two configurations of the DuraSeal Spine Sealant System.

Table 3-1: DuraSeal Spine Sealant System Components

Component	Description	Quantity
2 mL Configuration		
Polymer Kit		
Powder Vial 	Depyrogenated 10mL borosilicate glass vial containing 20,000 Da N-hydroxysuccinimide end capped PEG powder combined with FD&C Blue #1 as a visualization aid and BHT as a preservative. Vial is capped with a halobutyl elastomer (Santoprene®) stopper and Biodome BIO-SET® Injection Cap. The Biodome BIO-SET Injection Cap is a polyethylene and acrylonitrile/butadiene/styrene component that is attached to the Powder Vial and is used to pierce the vial seal (component purchased from Baxter Medical).	1 vial Approx 0.257 grams
Diluent Syringe	Polypropylene/polyethylene copolymer syringe containing sodium phosphate buffer (syringe purchased from Terumo Medical Corporation, cleared via K771205, 7/14/1977), capped with blue Santoprene end cap.	1 syringe Approx 1.3 mL
Clear Precursor Syringe	Polypropylene/polyethylene copolymer syringe containing Trilysine acetate in a sodium borate decahydrate buffer (syringe purchased from Terumo Medical Corporation, cleared via K771205, 7/14/1977), capped with white Santoprene end cap.	1 syringe Approx 1 mL
Plunger Cap	Plastic component that slides over both syringe plungers.	1
Syringe Holder	Plastic component that clips over both syringe barrels	1
Delivery System – Packaged Separately from Polymer Kit		
MicroMyst Applicator	Multi-lumen tube that provides separate channels for the flow of two non-homogenous fluids or solutions and filtered air from a compressed air source. The applicator delivers the two precursor solutions to the target surgical site.	1
Compressed Air Source – Provided Separately		
Flow Regulator (Non-sterile, Reusable)	Gas (i.e. air or nitrogen) regulator which provides filtered, compressed air/ gas to the MicroMyst Applicator	1
Air Pump (Non-sterile, Reusable) 	AC powered dry piston air compressor that provides filtered, compressed air to the MicroMyst Applicator	1

Component	Description	Quantity
5 mL Configuration		
Polymer Kit		
Powder Vial 	Depyrogenated 10mL borosilicate glass vial containing 20,000 Da N-hydroxysuccinimide end capped PEG powder combined with FD&C Blue #1 as a visualization aid and BHT as a preservative. Vial is capped with a halobutyl elastomer (Santoprene®) stopper and Biodome BIO-SET® Injection Cap. The Biodome BIO-SET Injection Cap is a polyethylene and acrylonitrile/butadiene/styrene component that is attached to the Powder Vial and is used to pierce the vial seal (component purchased from Baxter Medical).	1 vial Approx 0.5 grams
Diluent Syringe	Polypropylene syringe containing sodium phosphate buffer (syringe purchased from Tyco Healthcare Kendall, pre-amendment Class II device), capped with blue Santoprene end cap.	1 syringe Approx 2.7 mL
Clear Precursor Syringe 	Polypropylene syringe containing Trilysine acetate in a sodium borate decahydrate buffer (syringe purchased from Tyco Healthcare Kendall, pre-amendment Class II device), capped with white Santoprene end cap.	1 syringe Approx 2.5 mL
Plunger Cap	Plastic component that clips over syringe plungers.	1
Syringe Holder	Plastic component that slides over both syringe barrels	1
Delivery System – packaged within Polymer Kit Tray		
Dual Liquid Applicator, consisting of:	Plastic components that deliver the two polymer precursors to the target tissue	
Y-Applicator		1
Spray Tips		3

4.0 PROPOSED LABELING FOR THE DEVICE

DuraSeal Spine Sealant System

REF20-4300
REF 20-4004

Read Instructions for Use Prior to Using this Product.

Instructions for Use

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 Sealants composed of two solutions, a polyethylene glycol (PEG) ester solution and a trilysine amine solution (referred to as the 'blue' and 'clear' precursors, respectively). When mixed together, the precursors cross link to form the hydrogel sealant. The mixing of the precursors is accomplished as the materials exit the tip of the applicator.

The hydrogel Sealants naturally absorbed in approximately 4 to 8 weeks, sufficient time to allow for healing. The breakdown products are readily cleared from the body, primarily through the kidneys.

The DuraSeal 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). The polymer kits and applicators are provided sterile.

INDICATION

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

CONTRAINDICATIONS

The DuraSeal Spine Sealant System 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.

WARNINGS

- The safety and effectiveness of the DuraSeal hydrogel has not been studied in:
  - Patients with a known allergy to FD&C Blue #1 dye.
  - Procedures involving non-autologous duraplasty
  - 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 DuraSeal Spine Sealants 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 patient use only. Discard opened and unused product.
- Do not use if the PEG powder is not free flowing.
- Use within 1 hour of preparation.
- 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 breast feeding females
- Prior to application of the hydrogel, ensure that adequate hemostasis has been achieved.
- Incidental application of hydrogel to tissue planes that will be subsequently approximated, such as muscle and skin, should be avoided.

ADVERSE EVENTS

The DuraSeal Spine Sealant System was evaluated in a pivotal clinical Study, in which a total of 158 patients were enrolled (102 treated with DuraSeal Spine and 56 patients treated using Standard of Care 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. All Adverse Events were reviewed and adjudicated by an independent Clinical Events Committee (CEC), comprise of three independent neurosurgeons. The CEC's overall impression was that, within each treatment arm, the observed events appeared consistent in type and severity for the Study population.

[illegible]	[illegible]	[illegible]
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 (Incl 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)

Note: Patient can experience more than one AE

Further breakdown of the observed post-operative CSF leak and surgical site infection rates are presented in the tables below.

Presence of endpoint CSF leak within 90 days post-procedure	n (%)	8 (7.8)	3 (5.4)	0.748	13.2
CSF Fistula	n	3 (2.9)	0		2.9
Pseudomeningocele	n	5 (4.9)	3 (5.3)		10.2
Presence of SSI within 90 days post-procedure	n (%)	7 (6.9)	4 (7.1)	1.000	14
Deep Surgical Site Infection	n	5 (4.9)	1(1.7)		6.6
Superficial Surgical Site Infection	n	2 (1.9)	3 (5.3)		6.2

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

CLINICAL EXPERIENCE

A prospective, multi-center, randomized, two arm, single blind Study designed to assess if the DuraSeal Spine Sealant System, when used as an adjunct to sutured dural repair, is more effective than Standard of Care methods for producing a watertight dural closure in subjects undergoing an intentional durotomy during spinal surgery was conducted. Subjects that were scheduled for spinal procedures requiring a dural incision and who met the preoperative eligibility criteria were considered for Study participation. Subjects that met all of the intra-operative eligibility criteria were enrolled and randomized either to DuraSeal Spine Sealantor Control. The Study involved 24 investigational sites within the United States. A total of 102 patients were treated with the DuraSeal Spine Sealant, and a total of 56 patients were treated using Standard of Care methods to obtain a watertight dural closure.

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

Safety was assessed based on evaluation of the occurrence of post-operative CSF leaks and surgical site infection, the nature and severity of adverse events, protocol-specified laboratory tests, neurological assessments, and wound healing.

Inclusion/Exclusion criteria for the Study included the following:

Pre-Operative Inclusion Criteria:

- Subject was between 18 and 75 years of age.
- Subject was scheduled for a spinal procedure that entails a dural incision.
- Subject required a procedure involving surgical wound classification Class I/Clean (per CDC criteria).

- Subject, or authorized representative, was informed of the nature of the Study, and 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 closure, either spontaneously or upon Valsalva maneuver to 20 - 25 cm H_2O for 5-10 seconds

Intra-Operative Exclusion Criteria:

- Incidental finding of any of the pre-operative exclusion criteria.
- Subject required use of a synthetic or non-autologous duraplasty material.
- Subject had a gap of greater than 2 mm remaining after primary dural closure.
- Subject had undergone laminoplasty decompression.
- Subject had undergone a syringomyelia procedure where the shunt is not placed in the subarachnoid position.
- Subject had undergone a Chiari Malformation procedure that does not entail a dural incision at or below the C1 level.
- Investigator determined that participation in the Study may jeopardize the safety or welfare of the subject.

Demographic information for patients treated in the Study is shown in the table below:

[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)

Of the 158 subjects randomized, all 102 subjects (100.0%) treated with the DuraSeal Spine Sealant and 36 of the 56 subjects (64.3%) treated with Standard of Care methods displayed a watertight closure after assigned treatment. Three (3) subjects randomized to Standard of Care were considered not evaluable for the per protocol analysis of the primary efficacy endpoint, as the investigator chose not to use any of the Standard of Care methods per the protocol (i.e., devices designed to provide an intra-operative watertight closure).

Following the first DuraSeal Spine Sealant application, 93 subjects (91.2%) had a watertight closure upon Valsalva, while 9 subjects expressed a non-watertight closure. A second Sealant application was performed in all 9 subjects, following which all had a watertight closure upon second post-treatment Valsalva.

Within the Control arm, 35 subjects (62.5%) had a watertight closure upon Valsalva following the first Standard of Care application while 21 subjects expressed with a non-watertight closure. A second attempt with Standard of Care methods was attempted in 4 of the 21 subjects, at which time only 1 subject achieved a watertight closure upon second post-treatment Valsalva.

The number and 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 complex neurosurgical procedures performed. There were no deaths or unanticipated adverse device effects observed in the Study.

The incidence of protocol defined post-operative CSF leaks was comparable between the two treatment arms (7.8% vs. 5.4%, p= 0.748) despite that fact that the number of adjunctive therapies used in the Control subjects, following determination that subjects were a primary effectiveness endpoint failure, was greater. In fact, in **nineteen** Control subjects the primary dural repair was reinforced with buttressing materials such as synthetic duraplasty materials (i.e., dural graft matrix) or direct dural overlay of an absorbable sponge, see table below.

Further Adjunctive Therapy (ITT Population)

Parameter	Statistic	Control (N=56)
Number of Patients with Further Adjunctive Therapy		
Yes	n (%)	19(33.9)
No	n (%)	32(57.1)
NA	n (%)	5(8.9)
Material Used in Further Adjunctive Therapy		
Adhesive/Glue	n (%)	7(12.5)
Absorbable Gelatin Sponge	n (%)	5(8.9)
Dural Substitute	n (%)	1(1.8)
Dural Graft Matrix	n (%)	7(12.5)
Hemostatic Agent	n (%)	2 (3.6)
Other	n (%)	5(8.9)
Number of Materials Used in Further Adjunctive Therapy	n	19
	Mean	1.6
	Median	1.0
	SD	1.02
	Minimum - Maximum	1.0-4.0

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 Spine and Control arms, respectively, p=1.00). Although there were a greater number of deep surgical site infections within the DuraSeal Spine arm, two events occurred in subjects who were in fact ineligible for the Study due to factors that put them at higher risk for infection. One of these subjects was an uncontrolled diabetic and the other had undergone revision surgery for displacement of a lumbar interbody fusion device ("cage").
Furthermore, for another subject within the DuraSeal Spine 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 Spine arm becomes 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).

Overall, there were no clinically relevant differences in safety outcomes between the two treatment arms (DuraSeal Spine vs. Control) with respect to laboratory evaluations, neurological exams, vital signs, physical examination and wound healing. There was also **no difference between the two arms specifically with regard to CSF leak at 90 days.** 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 DuraSeal Spine Sealant, a potential concern when using hydrogel-based devices along the nerve roots. The data are consistent with the preclinical evaluation performed in a canine cauda equine discectomy model in which the DuraSeal Spine material (DuraSeal Sealant) was applied following lumbar discectomy, and exposure and abrasion of the lumbar nerve roots. In this severe model there were no significant neurological deficits noted and no adverse reactions were macroscopically observed for any of the dural Sealant treated sites.

DIRECTIONS FOR USE

DEVICE PREPARATION – 2 ML CONFIGURATION
REF 20-4300

A. Preparing the Blue Precursor

1. Remove the polymer kit tray and the MicroMyst Applicator from their respective outer pouches and introduce into the sterile field.
2. Remove lid from polymer kit tray.
3. Remove and discard syringe cap from Diluent Syringe (blue label).
4. Attach the Diluent Syringe to the Powder Vial.
5. Without depressing the syringe plunger, pierce the vial seal until it is fully depressed (twisting is not required). The entire threaded portion of the vial cap should be depressed bellow the level of the surrounding plastic vial rim.

6. Inject syringe contents into the vial.
7. Gently shake the vial/syringe assembly until the powder is completely dissolved.

8. Invert the vial/syringe assembly, and draw the vial contents back into the syringe.

9. Unscrew the syringe from the vial and discard the vial.
10. Remove syringe cap from Clear Precursor Syringe.
11. Ensure that the precursor volume in each syringe is equal.

B. Assembling the MicroMyst Applicator

1. Remove Applicator assembly from inner pouch.
2. Remove and discard the protective sheath over the Applicator shaft and tape from the Applicator air line.
3. Connect the Applicator air line to the compressed air source (Confluent Surgical Flow Regulator or Confluent Surgical Air Pump), and turn on air source.

4. Attach the Clear and Blue precursor syringes to the Applicator.

5. Attach the Syringe Holder (A) to syringe barrels and the Plunger Cap (B) to syringe plungers.

6. Applicator metal shaft and flexible tip may be angled to improve access or

DEVICE PREPARATION – 5 ML CONFIGURATION REF 20-4004

A. Preparing the Blue Precursor

12. Remove the polymer kit tray from its outer pouch and introduce into the sterile field.
13. Remove lid from polymer kit tray.
14. Remove and discard syringe cap from Diluent Syringe (blue label).
15. Attach the Diluent Syringe to the Powder Vial.
16. Without depressing the syringe plunger, pierce the vial seal until it is fully depressed (twisting is not required). The entire threaded portion of the vial cap should be depressed bellow the level of the surrounding plastic vial rim.

17. Inject syringe contents into the vial.
18. Gently shake the vial/syringe assembly until the powder is completely dissolved.

19. Invert the vial/syringe assembly, and draw the vial contents back into the syringe.

20. Unscrew the syringe from the vial and discard the vial.
21. Remove syringe cap from Clear Precursor Syringe.
22. Ensure that the

precursor volume in each syringe is equal.

B. Assembling the Dual Liquid Applicator

1. Attach the Clear and Blue precursor syringes to the Y-Applicator.
2. Attach the Syringe Holder (A) to syringe barrels and the Plunger Cap (B) to syringe plungers.

   Note:
   Avoid touching the plunger cap before application to avoid inadvertent precursor injection and tip plugging
3. Attach one Spray Tip to the Y-Applicator.

HYDROGEL APPLICATION
REF 20-4300, REF 20-4004

Note:

- Achieve hemostasis and minimize fluid (CSF, blood) outflow from the target site.
- Ensure that 2-3 mm margins around the defect edge are clear of blood clots, hemostatic reagents and/or loose connective tissue.

When using the MicroMyst Applicator:

1. Prime the Applicator by dispensing a small amount of hydrogel outside the target site until both precursors flow evenly.
2. Paint the target site with a thin coating of hydrogel by gently pressing the Plunger Cap until a thin layer, approximately 1 -2 mm in thickness, is formed.

   Note: Excess gel thickness should be avoided due to hydrogel swelling. Gel thickness should be limited to 1-2 mm. [do we really want to say this?
   Note: The blue color of the hydrogel aids in gauging thickness. As the thickness of the hydrogel increases to 2 mm, the fine epidural vasculature becomes less visible.

When using the Dual Liquid Applicator

3. Position the applicator 2-4 cm from the target site. Apply firm even pressure to the center of the plunger cap to dispense the precursors. Rapid initial spraying, followed by a slower controlled rate is recommended.
4. Continue applying the hydrogel until a thin (1 – 2 mm) coating is formed.
   Note: If delivery is interrupted and the spray tip is plugged, remove the spray tip, wipe the applicator tip, attach a new spray tip and continue delivery.

Note: The blue color of the hydrogel aids in gauging thickness. As the thickness of the DuraSeal hydrogel increases to 2 mm, the fine epidural vasculature becomes less visible.

5. Hydrogel application beyond the defect edges may be removed with scissors or mechanical disruption. Irrigation immediately after the Sealant has solidified is permitted.

STORAGE

The DuraSeal Sealant System should be stored at or below 77 °F (25°C).

SYMBOLS USED ON LABELING

[redacted]

②	**Do not reuse**
LOT	**Lot Number**
REF	**Catalog Number**
	Use by – year and month
LATEX	**Latex Free**
	See Instructions for Use
	Store below 25° C (77 °F)
STERILE R	**Sterile unless the package is damaged or open. Method of sterilization – *Radiation***
R_x only	Caution: Federal law (USA) restricts this device to sale by or on the order of a physician.

For more information, or to obtain Covidien documents or references, contact:
Covidien
101A First Avenue
Waltham MA 02451 USA
1-781-839-1700

DuraSeal is a trademark of Confluent Surgical, Inc. US Patents issued and pending

5.0 LITERATURE REFERENCES:

(1.) Camissa FP, Girardi FP, Sangani BA et al: Incidental Durotomy in Spine Surgery, Spine 2000;25;2663-2667

(2.) Hodges SD. Humphreys SC, Eck JC et al. Management of Incidental Durotomy Without Mandatory Bedrest Spine 1999;24:2062-2064

(3.) Narotam PK, Jose S, Nathoo N et al. Collagen Matrix (DuraGen) in Dural Repair: Analysis of a New Modified Technique Spine 2004; 29:2861-2867

(4.) deFreitas DJ, McCage JP. *Acinetobacter baumanii* Meningitis A Rare Complication of Incidental Durotomy J Spinal Disord Tech 2004;17:115-116

(5.) Morris GF. Marshall LF. Cerebrospinal Fluid Leaks: Etiology and Treatment-Complications of Spinal Surgery in *Spine Surgery*, Baltimore, Williams & Wilkins, 1733-1739

(6.) Wang J. et al Dural Tears Secondary to Operations on the Lumbar Spine: Management and Results After a Two-Year Minimum Follow-up of Eighty-eight subjects, J. Bone Joint Surg 1998 80A. 1728-1732

(7.) O'connor D, Maskery N et al. Pseudomeningocele Nerve Root Entrapment After Lumbar Discectomy, Spine 1998 23:1501-1502

(8.) Schumacher HW, Wassmann H et al: Brief Communication, Pseudomeningocele of the Lumbar Spine; Surg Neurol 1988;29:77-78

(9.) Friedman JA, Ecker RD, Piepgras DG, Duke DA. Cerebellar hemorrhage after spinal surgery: report of two cases and literature review. Neurosurgery. 2002 Jun;50(6):1361-3

(10.) Chueng-He Lu, Shung-Tai Ho et al: Intracranial subdural hematoma after unintended durotomy during spine surgery. Can UJ. Anesth 2002, 49:100-102

(11.) Bosacco SJ, Gardner MJ. Guille JT; Evaluation and Treatment of Dural Tears in Lumbar Spine Surgery. Clinical Orthopaedics and Related Research 2001; 389:238-247

(12.) Black P. Cerebrospinal fluid leaks following spinal or posterior fossa surgery: use of fat grafts for prevention and repair. Neurosurg Focus 2000 9: Article 4: 1-5

(13.) Eismont FJ, Weisel SW, Rothman RH. Treatment of dural tears associated with spinal surgery. J Bone Joint Surg [Am] 1981;63A:1132-1136

(14.) Rocca A, Turtas S, Pirisi A, Agnetti V. Iatrogenic lumbar pseudomenigocele, Zentralbl Neurochir. 1986;47(4):311-5

(15.) Shaffrey CI, Spotnitz WD et al: Neurosurgical Applications of Fibrin Glue: Augmentation of Dural Closure in 134 Subjects, Neurosurgery 1990; 26:207-210

(16.) Saint-Cyr M. Nikolis A. Moumdjian R. et al: Paraspinous Muscle Flaps for the Treatment and Prevention of Cerbrospinal Fluid Fistulas in Neurosurgery. Spine 2003;28:E86-E92.

(17.) Iskandar BJ, Fulmer BB, Hadley MN. Congenital tethered spinal cord syndrome in adults Neurosurg Focus 2001;10:1-5

(18.) Danish SF, Samdani A, Hanna A, Storm P, Sutton L. Experience with acellular human dura and bovine collagen matrix for duraplasty after posterior fossa decompression for Chiari malformations. J Neurosurg. 2006;104:16-20

(19.) Hawk MW, Kim KD. Review of spinal psuedomeningoceles and cerebrospinal fluid fistulas. Neurosurg. Focus 2000; 9: Article 5:1-5

(20.) Bryce GE, Nedzelsk JM, Rowed DW et al. Cerebrospinal fluid leaks and meningitis in acoustic neuroma surgery. Otolaryngol Head Neck Surg 1991; 104:81-87

(21.) Patel MR. Louie W, Rachlin J. Postoperative Cerebrospinal Fluid Leaks of the Lumbosacral Spine: Management with Percutaneous Fribrin Glue AJNR Am J Neuroraiol 17:495-500, 1996;

(22.) Nutik SL, Korol HW, Cerebrospinal fluid leak after acoustic neuroma surgery. Surg Neurol 43:553-7, 1995

(23.) McLain RF, Bell GR, Kalfas I, Tetzlaff JE, Yoon HJ Complications associated with lumbar laminectomy: a comparison of spinal versus general anesthesia Spine. 15;29:2542-7, 2004

(24.) Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emerg Med J 2001;**18**:205–207