2009-4437b1-01

FDA Executive Summary

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FDA Summary for DuraSeal Xact™ Sealant System

Plastic and Reconstructive Surgeries Devices Panel

May 14, 2009

FDA Executive Summary

INTRODUCTION

This is FDA's Executive Summary for Premarket Approval (PMA) application (P080013), Confluent Surgical's DuraSeal Xact Sealant System.

DEVICE HISTORY

The sponsor, Confluent Surgical, previously submitted and received agency approval for the DuraSeal™ Dural Sealant System (PMA P040034; approved on April 7, 2005) which is indicated for use as an adjunct to sutured dural repair during cranial surgery to provide watertight closure. The sponsor is now seeking premarket approval for use of the same PEG-based device in patients undergoing procedures in the spine.

The DuraSeal Xact™ Sealant System is intended for use as an adjunct to sutured dural repair during spinal surgery to obtain watertight closure. The chemical composition of the DuraSeal Xact Sealant precursors and, therefore, of the resulting hydrogel are identical to that of the DuraSeal Dural Sealant. This PMA has been reviewed by the Plastic and Reconstructive Surgeries Branch of the Division of Surgical, Orthopedic and Restorative Devices at the Center for Devices and Radiological Health of the Food and Drug Administration. Your time and effort in the review of this application is greatly appreciated.

The Executive Summary provides FDA's overview of the information provided by Confluent Surgical in P080013. The summary contains a rationale for bringing the device to Panel, an identification of the applicant/manufacturer, proposed indications for use, summary of the device description, non-clinical testing, and the clinical study information.

Rationale for Presentation of Duraseal Xact Sealant to the Panel

This brief section describes the rationale for presentation of this PMA to the Plastic and Reconstructive Surgeries Devices Advisory Panel.

In review of the application, 2 issues were raised which FDA believed were appropriate for discussion and input from a panel of experts. Firstly, the approved indication for use for DuraSeal (P040034), i.e., adjunctive use in cranial dura watertight closure, was considered inadequate to provide sufficient safety and effectiveness information to support an indication for use in spinal surgical procedures involving incision of the dura. Therefore, FDA believes use of the device in the spine represents a new indication for use. Secondly, the primary endpoint of the investigation, i.e., intraoperative assessment of sealing, is a surrogate evaluation for device clinical performance. FDA would appreciate Panel discussion and recommendations regarding the adequacy of this surrogate endpoint for determining device effectiveness. You will be asked to evaluate and discuss the presented data for the proposed indication and intended use, and to provide input regarding the interpretation of the safety and effectiveness results from the clinical study.

Applicant/Manufacturer Information

Applicant/Manufacturer Name and Address: Confluent Surgical, Inc. (dba Covidien)
101A First Avenue
Waltham, MA 02451, USA

Indications for Use

The applicant has proposed the following Indications for Use:

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

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

Please see the product information/instructions for use for a comprehensive listing of the device warnings, precautions and instructions for use as provided in the sponsor's summary or FDA's clinical summary

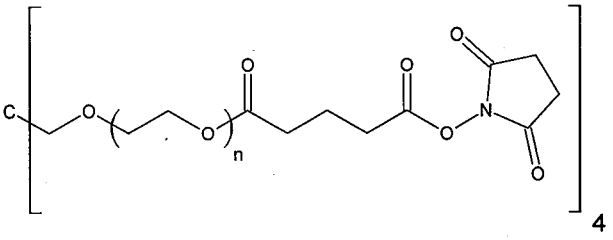
PRECLINICAL EVALUATIONS

DEVICE DESCRIPTION

The chemical composition of the DuraSeal Xact Sealant precursors and, the resulting hydrogel are identical to that of the DuraSeal Dural Sealant approved by FDA on April 7, 2005 under PMA P040034 and remain unchanged in this new PMA application.

The DuraSeal Xact™ Sealant System consists of components for preparation of an absorbable polyethylene glycol (PEG) hydrogel sealant and a delivery system (i.e., applicator, spray tips and plunger cap) packaged in a sterile single use kit. 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. When mixed together, the precursors provide rapid *in situ* polymerization via a nucleophilic substitution reaction to form a biocompatible absorbable hydrogel suitable for sealing the dura mater. The mixing of the precursors is accomplished in the DuraSeal delivery system as the materials exit the tip of the delivery system. The delivery system allows a conformal coating that 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 ester powder is N-hydroxy succinimide ('NHS'), end-capped polyethylene glycol (PEG) ester (i.e., PEG-SG) material. In the synthesis of the PEG-SG material, BHT is added as a preservative against free radicals in the PEG-SG powder (i.e., improve material stability). The structural formula for the PEG-SG material is shown below:

PEG-SG material structural formula



The molecule contains water sensitive ester linkages which allow it to hydrolyze within the body and resorb, but which also make it moisture sensitive during storage. In addition, the PEG backbone of this molecule is susceptible to oxidative chain scission. As such, the material is sensitive to moisture and elevated temperatures (see product specifications).

FD&C Blue no. 1 dye provides the color of the blue solution and enables the user to discern the thickness of the hydrogel layer and the area of hydrogel application. The gel swells, volummetrically, no more than 200%. For a 2 mm thick hydrogel that isotropically swells 200%, the maximum linear dimensional change in any direction is <1 mm. There is very little or no heat evolution during the polymerization reaction.

The following specifications define the device:

Table 1

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 hydrogel is visibly dissolved in 1.3 to 3.6 days after immersion into the phosphate buffered solution, pH of 7.4 at 60.4°C.
Buffer pH	Trilysine/Borate buffer pH is a determinant of gel time. Borate buffer pH is measured for the batch solution in production. Borate buffer pH in the individual syringes is monitored as a confirmation of the manufacturing controls.	The trilysine/borate buffer pH shall be between 10.01 and 10.37.
PEG Ester Vial Oxygen Content	Measures the oxygen content in the PEG ester powder vial. The PEG backbone is susceptible to oxidative chain scission, which can decrease the cross-link density of the material resulting in altered performance characteristics (i.e., increased gel times, increased swelling and shorter disappearance times).	The PEG Ester Vial Oxygen content shall be ≤ 1 %.
Gel application-pressure integrity	Test evaluates the mechanical joints of the applicator to ensure that the device is sufficiently robust to withstand anticipated use.	Applicators fluid lumens shall not leak or fail when pressurized to 68 psi for a minimum of 4 seconds.
Uniform gel application	Evaluates proper function of the applicator and mixing of the precursors to the target area to assure uniform sealant application.	Applicator disperses gel in a pattern < 10mm diameter when Spray Tip is 1-4cm from target tissue.
Biocompatibility	ISO 10993	The DuraSeal Spine Sealant meets the requirements of ISO 10993.

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 hydrogel implant is absorbed in approximately 4 to 8 weeks and the absorbed hydrogel components are excreted from the body primarily through the kidneys. The DuraSeal Xact™ Sealant can be used for up to one hour following reconstitution. The DuraSeal Xact Sealant is fully synthetic and contains no human or animal derived products and all components are provided sterile.

SUMMARY OF NON-CLINICAL STUDIES

The sponsor has evaluated the device, i.e., hydrogel sealant and device delivery system, using *in vitro* biocompatibility and in *vivo* safety and performance models. The biocompatibility determinations were done in accordance with the Federal Good Laboratory Practices Regulations (21 CFR § 58) and FDA's Blue Book memorandum G95-1 "Use of ISO-10993 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing". In addition, testing was conducted on the gel and delivery system to validate that the devices can be anticipated to perform as expected, and that the components are safe to use in the prescribed manner.

Biocompatibility evaluations
Sealant
Table 2

Test Reference	Method Reference	Results
Cytotoxicity (Agarose Overlay Method)	International Organization for Standardization: Biological Evaluation Medical Devices, Part 5. 10993-5: *Tests for Cytotoxicity*	Non-cytotoxic
ISO Maximization Sensitization Study (Guinea Pigs)	International Organization for Standardization: Biological Evaluation Medical Devices, Part 10. 10993-10: *Tests for Irritation and Sensitization*	Non-sensitizing
ISO Modified Intracutaneous Study	International Organization for Standardization: Biological Evaluation Medical Devices, Part 10. 10993-10: *Tests for Irritation and Sensitization*	No evidence of significant irritation
USP and ISO Modified Systemic Toxicity	International Organization for Standardization: Biological Evaluation Medical Devices, Part 11. 10993-11: *Tests for Systemic Toxicity*	No mortality or systemic toxicity
USP Pyrogenicity	International Organization for Standardization: Biological Evaluation Medical Devices, Part 11. 10993-11: *Tests for Systemic Toxicity*	Non-pyrogenic
Subchronic toxicity	This test evaluates the potential systemic toxicity of the test material following implantation in the rat.	No Systemic Toxicity
Bacterial Reverse Mutation Assay	International Organization for Standardization: Biological Evaluation Medical Devices, Part 3. 10993-3: *Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity*	Non-mutagenic
In Vitro Mammalian Chromosome Aberration Test	*In vitro* Chromosomal Aberrations Test evaluates the potential clastogenic properties of a test material solution.	Non-mutagenic
Micronucleus Cytogenic Assay in Mice	International Organization for Standardization: Biological Evaluation Medical Devices, Part 3. 10993-3: *Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity*	No clastogenic activity
In Vitro Mammalian Cell Gene Mutation Test	International Organization for Standardization: Biological Evaluation Medical Devices, Part 3. 10993-3: *Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity*	Non-mutagenic
ISO Muscle Implantation Study (2 Weeks)	International Organization for Standardization: Biological Evaluation Medical Devices, Part 6. 10993-6: *Tests for Local Effects after Implantation*	Slight Irritant
ISO Subcutaneous Implantation Study in the Rat (10 days)	International Organization for Standardization: Biological Evaluation Medical Devices, Part 6. 10993-6: *Tests for Local Effects after Implantation*	No significant macroscopic reaction. Microscopically material classified as non-irritant.
In Vitro Hemolysis (Modified ASTM-Direct Contact Method)	International Organization for Standardization: Biological Evaluation Medical Devices, Part 4. 10993-4: *Selection of Tests for Interactions with Blood*	Non-hemolytic
In Vitro Proliferative Effects of DuraSeal in Various Human Cancer Cell Lines	This test determines whether DuraSeal impacts the *in vitro* cancer cell growth (pro- or anti-proliferative effects) of 4 human cancer cell lines, HT29 Colon Cancer, OVCAR3 Ovarian Cancer, A549 Lung Cancer, and U-87 MG Gliobastoma. Cells were exposed to the test article for four days, after which time cell proliferation was assessed.	No proliferative or anti-proliferative effect. This assessment is very limited in scope and was not considered by FDA to provide definitive information regarding a potential stimulatory or inhibitory effect on transformed cells.

Chronic toxicity and carcinogenicity testing was considered un-necessary for the following reasons:

- There was no evidence of mutagenic or proliferative effects observed in the 4 genotoxicity/mutagenicity evaluations conducted
- The device chemical components/reagents are not known as carcinogens or considered to have potential mutagenic potential
- Exposure to the product is limited as the product is absorbed/degraded within 4-8 weeks of implant
- The metabolic pathway and rapid clearance of the PEG component material is well-studied
- The sponsor conducted animal model evaluations that, while not of the specific length of time specified in formal chronic toxicity evaluations, were adequate in length of time with respect to the anticipated presence of the device in humans

Delivery System - Biocompatibility

For medical externally communicating devices having tissue/bone contact of limited contact duration, cytotoxicity, sensitization and irritation evaluations are recommended. The sponsor conducted these assessments and found the components to be biocompatible.

Non-Clinical Safety Testing of Delivery Components

No performance standards or FDA guidance document specific to this type of device are available. Therefore, the sponsor identified key criteria for evaluation and conducted in vitro studies on the DuraSeal Xact Sealant System to assess the following:

- Identify key product specifications for assurance of product reliability
- Characterize performance of the MicroMyst Applicator and Dual Liquid Applicator delivery systems
- Assure that the DuraSeal Xact Sealant System is not compromised when exposed to extreme environmental conditions (i.e., freeze/thaw conditions and maximal E-beam irradiation exposure) – environmental testing
- Establish packaging integrity
- Establish an 18-month shelf life for the DuraSeal Xact Sealant System
- Sterilization validation
- Characterize performance of the DuraSeal Xact Sealant – animal studies
- Device component toxicology

Product specifications

Testing was conducted on test units that were manufactured in accordance with prespecified procedures and sterilized by the sterilization methods that will be used for production purposes (E-beam irradiation for the DuraSeal Xact Sealant System polymer kits and Dual Liquid Applicator; EtO sterilization for the MicroMyst Applicator).

Gel time and pot life, in vitro disappearance, swelling, borate buffer pH, and PEG ester vial oxygen content are designed to assess the functional performance of the DuraSeal Xact Sealant. These tests were performed to gather data to assess the viability of the base chemistry (i.e., reaction kinetics, the ability to cross-link and hydrolyze) and assure that the hydrogel precursors are not adversely affected by either the manufacturing or sterilization process.

Tests performed to assess key functional characteristics of the hydrogel and the purpose/rationale for each test are summarized in the Table below:

Table 3

Summary of Key DuraSeal Xact Sealant Tests

Parameter Evaluated	**Purpose/Rationale of Test**

Summary of Key DuraSeal Xact Sealant Tests

Parameter Evaluated	**Purpose/Rationale of Test**
Gel Time/Pot Life	Gel time is defined as the time it takes for a hydrogel to form when the two precursor components are brought into contact with each other and as such is a measure of the reaction kinetics. The ester component loses reactivity with time once reconstituted; the pot life assessment evaluates the gel time of the DuraSeal hydrogel after 1 hour following reconstitution of the blue precursor. The acceptance criterion for Gel Time/Pot Life is that, upon mixing precursors, a gel is formed in ≤ 3.5 seconds.
In Vitro Disappearance	The in vitro disappearance test evaluates the dissolution of the gel components while it undergoes hydrolysis in a simulated physiologic environment (phosphate buffered saline solution stored at elevated temperature). This test assesses the ability of the degradable PEG ester bonds to hydrolyze, and is performed using an accelerated test method, which evaluates in vitro disappearance of the hydrogel when immersed in phosphate buffered saline (PBS) maintained at 60.4°C. The acceptance criterion for material dissolution is between 1.3 and 3.6 days.
Swelling	Defined as the percent weight gain of a known mass of hydrogel resulting from 24-hour immersion in 37°C phosphate buffered solution. Serves as an indirect measure of the cross-link density (i.e., reduced cross-link density results in an increase in percent swelling). The acceptance criterion for in vitro swelling is ≤ 200%.
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 acceptance criterion for PEG ester vial oxygen content is ≤ 1%

MicroMyst Applicator and Dual Liquid Applicator delivery systems – performance criteria

The 2 mL and 5 mL configuration of the DuraSeal Xact Sealant System each include delivery system. Both delivery systems have been cleared via the premarket notification (i.e., 510(k)) process for indications for use consistent with use of the DuraSeal sealant.

The MicroMyst Applicator is a Class II device and has been cleared previously via K050998. The device is being used in accordance with its cleared indications for use statement:

Indication for use

510(k) Number (if known): K050998

Device Name: Confluent Surgical MicroMyst ™ Applicator and Air Pump

Indications For Use: The Confluent Surgical MicroMyst Applicator and Air Pump is indicated for use in the simultaneous delivery of two non-homogenous fluids or solutions onto a surgical site.

In addition, the Dual Liquid Applicator is also a Class II device, previously cleared via K042588 and it, as well, is being used in accordance with its cleared indications for use statement:

Indication for use

510(k) Number (if known): K061183

Device Name: Confluent Surgical Dual Liquid Applicator

Indications for Use: The Confluent Surgical Dual Liquid Applicator is indicated for use in the simultaneous delivery of two non-homogenous fluids or solutions onto a surgical site.

The 2 mL configuration contains the MicroMyst Applicator, an air assisted applicator, and the 5 mL configuration contains the Dual Liquid Applicator, a non air-assisted applicator. The applicators facilitate application of the precursor solutions onto the target surgical site. The MicroMyst Applicator and Dual Liquid Applicator are designed to mate, through luer-lock fittings, with the Diluent and Clear Precursor syringes of the DuraSeal Xact Sealant System polymer kits. To align the two precursor syringe barrels and to allow for simultaneous delivery of the two precursors in a 1:1 ratio through the applicator, a plunger cap is placed over the syringe plungers and a syringe holder is placed over the syringe barrels. The plunger cap and syringe holder components are provided within each of the polymer kit trays. Performance evaluation and determination of delivery reliability is essential for the safe and effective use of the product. Performance characteristic evaluations performed for the 2 delivery systems are summarized here:

Table 4

MicroMyst Applicator Functional Testing Results

<table>
<tr><th>Design Input</th><th>Specification</th><th>Results (n)</th></tr>
<tr><td>Applicator shaft can be bent to 45 degrees without compromising flow.</td><td>A minimum airflow of 0.15 L/min to must be achieved through the fluid lumens and a minimum airflow of 0.50 L/min must be achieved through the air lumen.</td><td>Pass (n=60)

Data Summary:

AirFlow L/min
<table>
<tr><th></th><th>Fluid Lumen</th><th>Air Lumen</th></tr>
<tr><td>Ave.</td><td>0.72</td><td>0.73</td></tr>
<tr><td>σ</td><td>0.02</td><td>0.07</td></tr>
<tr><td>Min.</td><td>0.68</td><td>0.60</td></tr>
<tr><td>Max.</td><td>0.75</td><td>0.83</td></tr>
</table></td></tr>
<tr><td>Verify that applicator lumens shall be free of occlusions, which prevent precursor flow</td><td>Air flow through air lumen shall be 0.50 L/min to 0.95 L/min @ 24 psi ± 5 psi. Air flow through fluid lumens shall be 0.15 L/min to 1.00 L/min @ 24psi ± 5 psi</td><td>Pass (n=60)

Data Summary:
<table>
<tr><th colspan="3">AirFlow L/min</th></tr>
<tr><th></th><th>Fluid Lumen</th><th>Air Lumen</th></tr>
<tr><td>Ave.</td><td>0.71</td><td>0.73</td></tr>
<tr><td>σ</td><td>0.03</td><td>0.06</td></tr>
<tr><td>Min.</td><td>0.50</td><td>0.60</td></tr>
<tr><td>Max.</td><td>0.78</td><td>0.83</td></tr>
</table></td></tr>
<tr><td>Verify that component channels are separate and independent</td><td>Fluid lumens channels shall be separate and independent.</td><td>Pass (n=60). All fluid lumen channels were separate and independent.</td></tr>
<tr><td>Verify solutions coverage</td><td>The applicators spray pattern must be < 10 mm in diameter when spray tip is 1cm from target tissue.</td><td>Pass (n=60)

Applicators produced a spray pattern less than 10 mm in diameter. The spray pattern on all applicators showed full atomization, no streaming of fluids was observed</td></tr>
<tr><td>Solutions mixing</td><td>The gel quality shall result in a score of 1 or 2 (where 1 = Good firm gel; 2 = Soft, but acceptable; 3 = Poor not acceptable)</td><td>Pass (n = 60)

Applicators produced a gel quality of 1 or 2</td></tr>
<tr><td>System shall allow up to 4 starts of the system without clogging</td><td>The applicator shall not clog after four starts and three stops while spraying.</td><td>Pass (n = 60)
Applicators did not clog after four starts and three stops while spraying.</td></tr>
<tr><td>Verify applicator fluid path for pressure integrity.</td><td>The fluid lumens shall not leak when pressurized at 68psi for 4 seconds</td><td>Pass (n = 60)
None of the applicators leaked when the fluid lumens were pressurized to 68 psi for 4 seconds.</td></tr>
<tr><td>Verify air lumen is free of leaks.</td><td>The air lumen shall not leak when pressurized at 40 psi for 4 seconds.</td><td>Pass (n = 60)
None of the applicators leaked when the air lumen was pressurized to 40 psi for 4 seconds.</td></tr>
<tr><td>Verify that the system delivers biomaterials without component failure.</td><td>The applicator shall not show any failures during normal use. No leaks, separation of components or cracks shall occur during use.</td><td>Pass (n = 60)
The applicators did not fail during normal use. No leaks, component failures, or cracks occurred during use.</td></tr>
</table>

Table 5

Dual Liquid Applicator Functional Testing

Design Input	Specification	Results (n)
Verify that the system delivers biomaterials without component failure.	The applicator shall not show any failures during normal use. No leaks, separation of components or cracks shall occur during use.	Pass (n = 60 Y-applicators) The applicators did not fail during normal use. No leaks, component failures, or cracks occurred during use.
Gel application-precursor cross-contamination: The polymer fluid lines at the spray tip must remain independent and intact to avoid premature cross linking of the hydrogel. This testing evaluates the spray tip for leaks and cross talk. The applicator has been tested for continuity under normal use conditions.	The two polymer precursor channels shall be separate and independent until mixing in the distal sprayer tip.	Pass (n = 60 Y-Applicators) All Y-Applicators withstood pressurizing of one channel for 5 second without fluid crossing between the chambers.
Gel application-pressure integrity: The applicator provides a delivery mechanism for the clear and diluent precursors to the application site. The applicator is designed to be compatible with open surgical procedures. The mechanical joints of the applicator must be sufficiently robust to withstand the anticipated use.	Applicator shall not leak or fail when pressurized to 68 psi for a minimum of 4 seconds.	Pass (n = 60 Y-Applicators) Pass (n = 90 Spray Tips) None of the components leaked when pressurized to 68 psi for 4 seconds.
Gel application-lumen continuity: Proper mixing of precursors is dependent on continuous and free flow.	Applicator lumens shall be free of occlusions, which prevent precursor flow.	Pass (n = 60 Y-Applicators) All Y-Applicators were free of occlusions.
Uniform gel application: The applicator is designed to provide atomization and mixing of the precursor streams as they exit the spray tip. Proper atomization and mixing of the precursors to the target area assures a uniform sealant. If the spray pattern is of sufficient size, there will be good mixing of the precursors, which in turn provides a well cross-linked hydrogel.	Applicator shall disperse gel in a pattern < 10 mm diameter when Spray Tip is 2-4 cm from target tissue.	Pass (n = 60 Y-Applicators) Pass (n = 90 Spray Tips) All components tested produced a spray pattern less than 10 mm in diameter.

Environmental testing

Environmental testing was conducted to ensure that the DuraSeal Xact Sealant System is not affected when exposed to the typically expected environmental conditions during storage and E-beam sterilization (i.e., freeze/thaw conditions and maximal E-beam irradiation exposure), testing was performed on the product after environmental conditioning.

The following testing activities were conducted:

- Freeze/thaw stability testing of the DuraSeal Xact Sealant and polymer kit components

The results provided indicate that all key product characteristics evaluated (i.e., gel time and pot life, in vitro disappearance and swelling) were within specification and equivalent to controls. Testing conducted demonstrates

that stability and functionality of the hydrogel was maintained under simulated worst-case environmental conditions.

- Performance testing of the MicroMyst Applicator after freeze/thaw conditioning
- Performance testing of the Dual Liquid Applicator after freeze/thaw conditioning

Test results indicate that the Dual Liquid Applicator (i.e., Y-Applicator and spray tip) functions as intended when sterilized and stored under the typical processing conditions of a polymer kit.

- Performance testing of the DuraSeal Xact Sealant System polymer kits after exposure to high irradiation doses

Results provided for the 2 mL DuraSeal Xact Sealant System polymer kit maximum radiation dose study demonstrate that the kit passed the acceptance criteria specified.

Packaging/packaging integrity

The DuraSeal Xact Sealant System polymer kit is provided in a terminally sterilized package that contains the components for preparation of the DuraSeal Xact Sealant.
Each 2 mL DuraSeal Xact Sealant System polymer kit (P/N 70-2006-001) contains the following components:

•PEG ester powder vial with Biodome BIO-SET injection cap
•Diluent syringe with pre-attached blue end cap
•Trilysine amine solution (clear precursor) syringe with pre-attached white end cap
•Syringe holder
•Plunger cap

Each 5 mL DuraSeal Xact Sealant System polymer kit (P/N 70-2005-122) contains the following components:

•PEG ester powder vial with Biodome BIO-SET injection cap
•Diluent syringe with pre-attached blue end cap
•Trilysine amine solution (clear precursor) syringe with pre-attached white end cap
•Syringe holder
•Plunger cap
•Y-Applicator
•Spray tips (3)

The above components are placed into a polyethylene terephthalate-glycol (PETG) tray and sealed using a heat sealer. Following sterilization, the polymer kits are shipped to Millstone Medical Outsourcing, a contract packaging/labeling and distribution facility (FDA Est. Reg. No.: 1226544). The final labeling and packaging operation of the polymer kits into Finished Goods is completed at Millstone Medical Outsourcing.

For delivery to the customer of the DuraSeal Xact Sealant System 2 mL configuration,
one (1) sterile pouched 2 mL polymer kit (P/N 70-2006-001) and one sterile double pouched MicroMyst Applicator (P/N 70-2007-001) are placed into a shelf-box. The product is cold-shipped to the customer in quantities of up to 3 or up to 6 each (i.e., 1 small insulated shipper box containing up to 3 shelf boxes or 1 larger insulated shipper box containing up to 6 shelf boxes, each shelf box containing 1 sterile pouched 2 mL polymer kit and 1 MicroMyst Applicator).

For delivery to the customer of the DuraSeal Xact Sealant System 5 mL configuration, five (5) sterile pouched 5 mL polymer kits (P/N 70-2005-122) are placed into a shelf-box. The shelf-box is 0.024" thick Solid Bleached Sulfate material. The product is cold-shipped to the customer in quantities of up to 2 or up to 5 each (i.e., 1 small

insulated shipper box containing up to 2 shelf boxes or 1 larger insulated shipper box containing up to 5 shelf boxes, each shelf box containing 5 sterile pouched 5 mL polymer kits).

The sponsor has conducted studies to verify that the packaging materials and configuration are acceptable for use. The following testing activities were conducted and results are provided:

- Accelerated Aging of the Packaging Pouch, Tray and Tyvek Lid

Test data demonstrate that the packaging materials are acceptable for use and it has been established that packaging integrity and adequate seal strength is maintained over at least 18 months of shelf life.

- Ship Testing in accordance with International Safe Transit Association (ISTA 1A) Vibration and Drop Testing of the final shipment packaging

The test data demonstrated that the packaging is suitably designed to protect the DuraSeal Xact Sealant System during transport.

- Microbial Challenge of the Packaging Pouch and Polymer Kit Tray Tyvek Lid

Data from these studies demonstrate that the packaging pouch and tyvek lid materials selected are effective microbial barriers and are appropriate for the intended use.

- Packaging Pouch and Polymer Kit polyethylene glycol (PEG) ester Tray Porosity Testing

Data from these studies demonstrate that the material selected for the film side of the packaging pouch and for the tray are effective microbial barriers and are appropriate for the intended use.

Shelf Life Testing

The DuraSeal Xact Sealant System will be labeled with an 18-month expiry date. The 18-month shelf-life is based on the results of several studies that evaluated the stability of the DuraSeal Xact Sealant and the individual components of both 2 mL and 5 mL DuraSeal Xact Sealant System polymer kits. The 18-month shelf life is based upon real time aging as established for the currently marketed DuraSeal Dural Sealant System. In previous validation for the comparison of real time aging with accelerated aging test data, it was established that an accelerated aging factor of 3X allows for the use of accelerated aging data to establish shelf life. The data provided showed that all key attributes evaluated (i.e., integrity, gel time at 1 hour post-reconstitution, in vitro disappearance, swelling, and packaging integrity) were within specification at t = 0 and through 80 weeks of storage at 25 °C/60% RH, and through 28 weeks of storage at 35 °C/75% RH. The information provided supports an 18 month shelf life expiration date.

Sterilization Validation

Sponsor has conducted the following sterilization validation activities:

- E-beam irradiation sterilization to a Sterility Assurance Level (SAL) of 1 x 10-6, validated in accordance with "AAMI/ANSI/ISO11137:1995(E), Sterilization of health care products –Requirements for validation and routine control – Radiation Sterilization", "EN 552:1994
- Sterilization of medical devices - Validation and routine control of sterilization by irradiation", "AAMI TIR No. 27:2001,
- Sterilization of healthcare products – Radiation sterilization – Substantiation of 25 kGy as a sterilization dose, Method VDmax", and "ANSI/AAMI/ISO 11737-1:1995,
- Sterilization of medical devices – Microbiological methods – Part 1: Estimation of the population of microorganisms on products".

Animal testing – sealant performance

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

Table 6

ımmary of Animal Studies

Test Performed	**# Animals/ Study Duration**	**Summary/Relevant Findings**
Dural Sealing in a Canine Cranial Model	13 test (hydrogel) and 13 control/56 days	Study performed to demonstrate both safety and effectiveness of the hydrogel as a dural sealant. Study endpoints included sealing capability of CSF leaks after treatment with the hydrogel ("test") when compared with control ("no treatment") following challenge with a Valsalva maneuver, and confirmation of normal healing (tolerance) following application of the hydrogel. In this study a 2 cm incision of cranial dura and arachnoid was created in 26 adult dogs and loosely repaired (microsutures). The device was applied over the 2 mm dural gap in 13 dogs; 13 control dogs did not have hydrogel application. Postoperative survival was for 1, 4, 7 or 56 days when valsalva test and histopathology was obtained on 3 animals per cohort. Animals were observed to qualitatively assess normal behavior, general health signs (e.g., incision healing, appetite), and for possible CNS abnormalities. Results: All dogs remained neurologically intact. At re-exploration, 11/11 control dogs showed CSF leakage at < 20 cm H_2O – ambient pressure, while 1/12 treated dogs showed CSF leakage due to a faulty seal application but none showed CSF leakage at ambient pressure (ambient pressure is defined as 5 cm H_2O; normal CSF pressure in dogs is reported to be approximately 9 cm H_2O). Marked peridural adhesions were encountered in 3/3 control dogs at 7 days, and 1/3 control dogs at 56 days; no dural adhesions were observed in the treated group. Valsalva at 1, 4, 7 and 56 days showed mean leakage pressures of, respectively: 5, 5, 7 and 13 cm H_2O in controls and 53, 37, 42 and 48 cm H_2O 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. The device appeared elastic, strong, and tenaciously adherent to the dura, and complied with the sustained dural pulsations induced by artificial increases of intracranial pressure. Evidence of residual implant material was less evident at the 7 day re-explorations, and had completely disappeared by 56 days. None of the dogs showed evidence of epidural mass effect, epidural or subdural hematomas, infection, or unusual inflammatory reaction.
Hydrogel Appearance ınder MR and CT maging	2 test (hydrogel)/14 weeks	An evaluation was undertaken to determine the MR and CT imaging characteristics of the hydrogel following implantation. Additionally, histological evaluation was performed to evaluate for potential local toxicity and/or space filling defect. Following a craniotomy in 2 dogs, DuraSeal was sprayed onto the dura (3 mm in thickness), i.e., the dura was not incised, 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. Gel appearance at each time point was characterized, and compared with pathological findings obtained 14 weeks following implantation. Both dogs remained neurologically intact. The sealant was readily apparent with both imaging techniques out through 6 weeks. Absorption of the gel and subsequent closure of the remaining void was observed. The investigators found that the sealant could be viewed with MRI and CT and could be distinguished from CSF. Histological examination found an unremarkable response with no neurotoxicity noted nor space filling defects observed. Histological examination 14 weeks following implantation found normal bone flap healing, very little scar formation between the bone flap and dura and no dura mater/pia mater adhesions. The underlying cerebrum was normal with no evidence of toxicity. The outline of the cerebrum was normal with no compressive alteration or evidence of a local mass effect. With MRI/CT imaging, the investigators noted the following resorption characteristics (important observations in that they mirror other preclinical persistence/degradation/resorption evaluations): • "there is a rapid reduction in hydrogel volume between weeks 2 and 4 simultaneous with a reduction in marginal enhancement intensity. There is a gradual ongoing reduction in the volume of hydrogel and the conspicuity of the hydrogel-adjoining enhancement, until the 10 week time point, when there is near total resorption with virtually no residual enhancement."

Test Performed	# Animals/ Study Duration	Summary/Relevant Findings
		• With regard to differentiating the appearance of the gel in contrast to CSF, inflammatory collections or an infected surgical bed, the examining clinician stated that: the gel collection is hyperintense to CSF, inflammatory collections would be expected to have greater signal heterogeneity, and that the symmetric and homogenous circumferential marginal enhancement should be helpful, respectively, to interpretation of the image.
mplantation of Hydrogel n Rat Brain Parenchyma	8 test (hydrogel) and 8 control/42 days	The test article was implanted in brain tissue of the rat. The material was evaluated for the potential to cause systemic toxicity and the tissue was evaluated for evidence of local irritation or toxicity at the implant site. The test article was cut into 1 mm x 1 mm x 1 mm sections as were control materials, absorbable gelatin sponge and fibrin sealant. Detailed examinations for clinical signs of disease or abnormality and a neurological assessment were conducted on days 4, 15, 28 and 42. The brain, the implant sites and spinal cord were examined macroscopically. Macro and micro-scopic evaluations of the implant sites were conducted to define any tissue response. Under the conditions of the study, animals were healthy over the course of the study, no neurologic deficits were noted and no adverse reactions were macroscopically observed for any of the test or control sites at explant. The microscopic evaluation indicated there was no evidence of a local irritancy effect or a neurotoxicity effect in association with the test article implanted within the neuropil of the brain in rats. All alterations observed were consistent with surgical induced trauma or represent the normal tissue healing response to a space-occupying mass or cavitating lesion within a narrow area of the brain. The test article would be considered an inert space occupying mass that did not induce a local irritant or neurotoxic response in any of the sections of the brain evaluated.
Neurotoxicity Study in he Rat Following njection into the Brain	13 test (hydrogel) and 13 control/2 weeks	The potential neurotoxicity of the hydrogel compared to a control solution was evaluated following injection of prepared extracts into the lateral ventricle and the cisterna magna of the brain of a rat. Detailed health examinations and neurologic assessments were conducted at prespecified intervals. At 4 days and 2 weeks following injection, half of the animals from each cannulation type and treatment group were euthanized and necropsy performed. No macroscopic encapsulation was observed at any test or control cannulation site. The microscopic evaluation of the tissues revealed no evidence of a treatment related response.
Evaluation of Hydrogel Persistence Following Subcutaneous mplantation in the Rat	21 test (hydrogel) and 21 control/14 weeks	The results of this study document that in vivo absorption of the hydrogel is complete within 8 weeks of implant. The hydrogel to be used in the spine is identical in chemical composition to the hydrogel evaluated in this study. Study performed to evaluate the *in vivo* persistence and degradation of the hydrogel over a period of 14 weeks following subcutaneous implantation in the rat. Results demonstrate that the hydrogel persists essentially in its initial form for 2 weeks, becomes noticeably softer at 4 weeks and is predominantly degraded by 6 weeks.
Study for Effects on Embryo-Fetal Development in Rats Following Intraperitoneal Administration	25 test (hydrogel) and 25 control/2 weeks	Study performed to determine the developmental toxicity, including the teratogenic potential of the hydrogel in rats following subcutaneous administration on Day 6 of gestation. Detailed clinical observations were performed daily up through 20 days of gestation. Dams were subjected to necropsy including uterine examination and fetuses were evaluated for malformations and developmental variations. No toxic or teratogenic observations were noted comparing the sealant to a control substance. Based on the results of this study, the No Observable Effect Level (NOEL) for maternal and developmental effects is >0.1 mL (0.3909 mL/kg) of hydrogel, which represents almost 5.5 times the anticipated exposure under normal conditions of use. Under the conditions of this study, the hydrogel was found to be non-teratogenic in rats.
Canine Lumbar Laminectomy Study	13 animals, two surgical sites per animal: treatment (hydrogel) or surgical control (no treatment)/12 - 14 weeks	Study was performed in a canine lumbar laminectomy model. Following laminectomies at L3 and L5, the two surgical sites were randomized to either hydrogel treatment or control. 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. One animal was terminated early due to a loss of function in their hind limbs following surgery. Histopathological examination

Test Performed	# Animals/ Study Duration	Summary/Relevant Findings
		revealed that the animal had an abscess at the incision site. Fluid was removed from the incision sites of other animals due to inflammation signs but no micro-organisms were identified. The device was found to decrease the severity and incidence of periosteal-dural adhesions: 4/6 control animals had complete adhesion formation whereas only 2/6 DuraGel-treated animals had complete adhesion formation. Use of the device resulted in a 42.4% reduction in scar area in comparison to control. The general health of the animals remained excellent throughout the study. Other than the one that had to be euthanized, no animals exhibited neurological, behavioral or health problems. The extraspinal tissue had healed normally, and both the treated and control sites exhibited the same amount of bone regrowth. Gross pathological and histopathological examinations showed that the hydrogel decreased the severity and incidence of periosteal-dural adhesions.
Cauda Equina Study in the Canine	9 animals each assigned to treatment group (hydrogel) or surgical control (no treatment)/8 weeks.	Study was performed in a canine cauda equina discectomy model to assess the acute and subchronic dural sealing as well as adhesion prevention when DuraSeal was applied to the lumbar region following spinal surgery. The hydrogel was applied to the lumbar region following spinal surgery using a fine air-assisted sprayer (i.e., MicroMyst Applicator). The fine-air assist applicator was assessed for performance with regard to thickness and volume of material delivered to the confined spaces of the spinal canal. Eighteen dogs were assigned to either treatment or control groups. Following exposure of the cauda equina, the nerve roots were lightly abraded and a partial discectomy was performed. 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. 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. The air pump/misting apparatus delivered a consistent amount and thickness of the material.

Device component/reagent toxicology

Chemistry/Toxicology

The manufacturing components of DuraSeal are:

- Water for injection
- PEG ester
- Trilysine
- Sodium borate decahydrate
- Sodium phosphate
- FD&C Blue #1 dye
- Butylated hydroxytoluene (BHT).

The breakdown products are essentially the same:

- Water
- PEG
- Trilysine
- Sodium borate
- Sodium phosphate
- FD&C Blue #1 dye
- BHT
- N-hydroxy succinimide

When asked what a worst case exposure scenario would be for a cranial-based surgical procedure, the sponsor cited clinical experience in Europe that indicates that up to 5 grams of sealant may be used for a typical surgical procedure. This quantity of the device provides a 2 mm thick film covering a surface area of 25 cm^2. In a 70 Kg patient the amount of the device administered would be 71.4 mg/Kg. The various chemicals identified in the product have toxicities only associated with exceptionally large doses. The anticipated dose of each chemical anticipated in humans is far below the published toxicity values. The sponsor investigated large excess of these chemicals in various animal preclinical studies and in 4 mutagenicity/genotoxicity evaluations. No toxic findings were noted. In addition, none of the reagents are identified as carcinogens and some have had "limits of exposure" established by EPA, e.g., EPA has set a limit for exposure to Toluene of 1 mg/L of drinking water.

The DuraSeal Xact Sealant contains FD&C Blue #1 dye for visualization of the hydrogel during application. The dye is a certified color listed in 21 CFR 82 and it has been approved for use in foods (21 CFR 74.101), drugs (21 CFR 74.1101) and cosmetics (21 CFR 2101). FD&C Blue #1 is water soluble and has been evaluated in life-exposure animal studies that determined an acceptable daily intake (ADI) for the dye of 12 mg/kg/day. Calculations comparing the amount of dye absorbed by ingestion, and the amount of dye a patient will be exposed to in one application of DuraSeal Xact Sealant, indicate that the absorbed amount of ingested dye would be much greater, and accepted as safe, by ingestion. In vitro and in vivo determinations found low microgram/mL concentrations after 9 hours of elution from polymerized gel in a saline bath or undetectable amounts (low microgram detection sensitivity) of the dye at 7-8 days, post-implantation in a dog model. The dye was determined to not be present in the body for a significant amount of time. Animal model evaluations of the device as intended to be used, i.e., placed on the dura of canine cranial and spinal evaluations, did not reveal site-specific toxicities. In addition, the clinical protocol specified that renal function, a potential target of PEG metabolism toxicity, would be monitored via BUN and creatinine laboratory determinations.

SUMMARY OF FDA REVIEW OF PRE-CLINICAL DATA

The sponsor initiated their regulatory submission pathway with Investigational Device Exemption (IDE) application #G050063 to investigate the effectiveness and safety of their dural sealant product for use in spinal surgical procedures. The device is the same product that was reviewed and approved via P040034, the DuraSeal™ Dural Sealant System. The sponsor submitted modular PMA application #M070001 which identified manufacturing, preclinical/non-clinical and clinical modules. A deficiency letter regarding the preclinical module/information was sent to the sponsor requesting additional information for 2 issues:

Issues Raised during the review of animal biocompatibility/toxicity data:

Although an initial review of the animal biocompatibility/toxicity studies found the information provided and the testing activities adequate, upon further consultation with the clinical staff it was noted that the animal model had assessed the device's performance in a lumbar anatomic application, but did not include assessment in the cervical spine location. The clinical concerns were communicated to the sponsor via an AI letter issued on August 31, 2007.

Below is a brief summary of the deficiency questions and the sponsor's response:

1. Animal Studies

In your animal studies you presented 2 canine spine models. You tested animals in a lumbar laminectomy model and 9 in a cauda equina model. The studies were performed with appropriate controls and showed no neurological or other significant adverse events. However, the lumbar spine is significantly different in anatomical considerations as compared to the cervical or thoracic spine (e.g. spinal cord underlies the cervical and thoracic thecal sac as compared to nerve roots in the lumbar thecal sac). Your intended use statement states: "*The DuraSeal Xact Sealant System is intended for use as an adjunct to sutured dural repair during spinal surgery to provide watertight closure.*" Therefore, please provide animal data to support the safety of your device in the cervical and thoracic spine.

Review of Response to deficiency question# 1:
Clinical Reviewer (neurosurgeon) Comments:

The sponsor states that the canine spine is different in anatomical considerations as compared to the human spine. While the spinal cord in humans typically ends at about the level of the L1/L2 vertebrae, resulting in primarily nerve roots under the lumbar thecal sac, spinal cord is present under the lumbar thecal sac in canines.

[The] sponsor has provided pictorial evidence, a schematic representation of the typical relationship between spinal cord and vertebrae for medium sized and large dogs. The schematics show that the spinal cord is present under the thecal sac until at a minimum the level of the L5 vertebra, similar to what is found in human cervical and thoracic spine.

The sponsor also states that the Canine Laminectomy Study reported in the submission, involved L3 and L5 vertebrae. [The] sponsor has provided representative gross histology images for various cross sections through the lumbar region of both control (no treatment) and hydrogel treated dogs evaluated under this study which show that spinal cord was present at the L3 and L5 vertebrae. Sponsor states that results obtained from this study demonstrated that the DuraSeal Xact Sealant performs as intended when used in an animal model that is representative of the human thoracic and cervical spine, as none of the animals exhibited neurological or behavioral problems, or evidence of neurological lesions.

2. Warnings

In the warnings section (section3.5), the following warning is provided: "Do not use the DuraSeal Xact Sealant System as 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." There is also a precaution stating: "Prior to application of the Spinal Sealant hydrogel, ensure that adequate hemostasis has been achieved." Many surgeons would not use DuraSeal as a hemostatic agent, but it can function as such. When using this product as a hemostatic agent it also functions as void filler. The risk profile of this use increases in cervical and thoracic spinal applications. Please include a warning against the use of DuraSeal Xact Sealant System as a hemostatic agent in your warning section and in the product labeling.

Review of Response to deficiency question#2:
Clinical Reviewer Comment:

The sponsor reiterates that the subject device is not designed nor intended to be used as a hemostatic agent. The sponsor states that the sealant is intended to be used as an adjunct to sutured dural repair during spinal surgery to provide watertight closure, which involves ensuring that adequate hemostasis has been achieved prior to application of the sealant. The sponsor indicates that they will include appropriate language against the use of the subject device as a hemostatic agent in the product labeling and that the following warning will be included in the subject device's Instructions for Use: "Do not use the DuraSeal Xact Sealant System as a hemostatic agent".

In summary review of the requested information:

- The sponsor's response to the AI letter was reviewed and found to be adequate
- The Pre-Clinical Data Module (M07001/M002) was accepted and closed in December 2007.

Summary of animal biocompatibility/toxicity evaluations

- The *in vitro* and animal biocompatibility/toxicity tests were conducted properly, had the appropriate controls, and generated valid data.
- A finding of "slight irritation" in the muscle implantation test is probably due to physical displacement caused by inserted gel slabs.
- Endotoxin content is quite low and would not be expected to stimulate inflammation.
- The few of observations of localized, transient foci of macrophages are readily explained by normal tissue reaction to any material in the process of being absorbed over a period of 4-8 weeks.
- The only remarkable differences from controls observed in the presence of the PEG hydrogel was slight/transient displacement of some tissue (with no neurological sequelae), desired sealing of

surgical openings in the dura, decreased tissue adhesions, increased nerve root mobility, and decreased scarring.
- The results presented in the biocompatibility/toxicity studies support the sponsor's claim that the hydrogel is biocompatible, does not induce unusual inflammation, and is non-neurotoxic.

SUMMARY OF PRECLINICAL TESTING

The sponsor, Confluent Surgical, previously submitted and received agency approval for the DuraSeal™ Dural Sealant System (PMA P040034; approved on April 7, 2005) which was indicated for use as an adjunct to sutured dural repair during cranial surgery to provide watertight closure. The sponsor is now seeking premarket approval for use of the same PEG-based hydrogel (referred in the present submission as the DuraSeal Xact Sealant System) in patients undergoing procedures in the spine.

- The chemical composition of the DuraSeal Xact Sealant is identical to the DuraSeal Dural Sealant system (approved by FDA on April 7, 2005 under PMA P040034).

- The sponsor has provided Pre-Clinical testing information as agreed upon in PMA Shell M070001

- Results and data from in vitro testing show that the design output requirements of the DuraSeal Xact Sealant System components meet design input requirements.

  - A series of *in vitro* tests were performed on the components and materials of the DuraSeal Xact Sealant System (final, finished, sterilized devices).
  - The sponsor has provided satisfactory test results for key parameters, with regards to material characterization and in vitro testing: Gel Time and Pot Life, In vitro Disappearance, Swelling, Buffer pH, PEG Ester Vial Oxygen Content

- Consistent functional performance for three production lots of the 2 mL and 5 mL DuraSeal Xact Sealant System polymer kits has been demonstrated.

- Environmental testing was performed to assure that the product is not affected by temperature extremes or maximum irradiation dose:

  - Environmental studies have been provided to support the viability of the base chemistry, and to verify that the DuraSeal Xact Sealant is not adversely affected by the manufacturing or sterilization process.
  - Materials selected for packaging of the DuraSeal Xact Sealant System have been demonstrated to be suitable for their intended use.

- Studies and data to support an 18-month shelf life have been provided--based on product performance testing of the DuraSeal Xact Sealant and evaluation of system components and packaging. Shelf life was derived from test results obtained on products stored under a variety of conditions, reflecting both real-time and accelerated aging.

- Biocompatibility and toxicity testing information provided is considered adequate

- There are no outstanding safety and effectiveness concerns with regards to the pre-clinical testing data provided in support of the proposed new indication. The pre-clinical testing conducted is considered adequate.

CLINICAL EVALUATIONS

Overall Clinical Study Description:

The applicant has presented data from a prospective, multi-center, randomized, two-arm, single blind clinical investigation designed 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 (SOC) methods (control) for producing a watertight dural closure in subjects undergoing an intentional durotomy during spinal surgery. The study involved 158 patients treated at 24 investigational sites within the United States. A total of 102 subjects were treated with the DuraSeal Spine Sealant, and a total of 56 subjects were treated using SOC (Control) methods. Previously, the sponsor had conducted a prospective, multi-center, non-randomized, single arm clinical investigation to evaluate the safety and effectiveness of the same dural sealant as an adjunct to sutured dural repair during cranial surgery. The study involved 10 investigational sites within the United States and 1 site in Europe with a total of 111 patients being treated with the dural sealant. DuraSeal for the cranial indication was approved in the U.S. in 2005. For the spine indication for use, an IDE (G050063) was initiated in April, 2005.

Clinical Device Evaluation History and Overall Study Objectives:
Prior to the sponsor's spinal CSF leak prevention study, two clinical evaluations were performed to evaluate the safety and performance of the dural sealant as an effective sealant providing watertight closure in patients scheduled for elective cranial surgeries:

- European pilot study – 45 cranial and 2 spinal patients
- US pivotal study (P040034, approved in April, 2005 – 111 patients at 10 U.S. sites and 1 European site; all cranial

A prospective, single center, non-randomized clinical investigation to evaluate the safety and performance of the DuraSeal Dural Sealant System in patients scheduled for elective cranial or spinal surgery was performed in the Netherlands. A total of 47 patients were treated with the DuraSeal Dural Sealant System; 45 (95.7%) cranial and 2 (4.3%) spinal intra-dural procedures. The primary endpoint of this study was a reduction in the incidence of intra-operative cerebrospinal fluid (CSF) leakage following dural sealant application defined as no CSF leakage from dural repair intra-operatively during Valsalva maneuver (20 cm H_20). None of the 47 patients treated with the DuraSeal System demonstrated a CSF leak during the post application Valsalva maneuver, thus demonstrating a 100% success rate in holding an immediate watertight seal. The incidence of clinically diagnosed post-op CSF leaks was 4.7%, the incidence of pseudomeningocele was 2.3%. The primary safety endpoint was defined as procedure-related complications and adverse events. There were a total of 51 adverse events reported in 28 patients; there were 14 serious adverse events in 11 patients or an overall incidence of 29.8% in the study. None of the reported adverse events were deemed by the investigator or sponsor as related to the DuraSeal System.

In the U.S. clinical investigation of the device for the cranial indication, a 98% rate of water tight closure as tested by a Valsalva maneuver to 20 cm of water pressure immediately after DuraSeal application was observed. The results demonstrate that the device is effective at providing a water-tight dural closure in cases where suturing alone, or in combination with autologous grafting is not successful. In considering the clinical benefit of the device, FDA concurred that achieving a watertight closure of the dura is recognized as an important step in preventing post-operative CSF leaks. The overall rate of surgical wound infection was 9/111 (8.1%) with a 7.2% rate of deep surgical infection, all requiring repeat surgery. The overall rate of CSF leak was 4.5% (5/111). The rates of these complications were within the ranges reported in the literature for patients with similar risk factors who underwent craniotomies. The rates of other serious adverse events were comparable to expected outcomes of intracranial surgeries. FDA and the Neurological Devices Advisory Panel determined that further evaluation of risk factors for these events should be assessed in a Post-Approval Study (PAS).

In conclusion, FDA found that the results from preclinical studies indicated that the DuraSeal Dural Sealant System met or exceeded safety and performance specifications. Data collected from a multi-center clinical investigation of the performance of the DuraSeal Dural Sealant System provided a reasonable assurance of product safety and effectiveness when the device is used, in accordance with the labeling, as an adjunct to sutured dural repair during cranial surgery to provide watertight closure.

The purpose of the study under current panel consideration was to evaluate the safety and efficacy of the Spinal Sealant as an adjunct to sutured dural repair compared with standard dural closure techniques (SOC/control) to obtain watertight closure in patients undergoing spinal surgery.

Study Design

Patients who were scheduled for an elective spinal procedure that required a dural incision and who met pre-operative study eligibility criteria were eligible to participate in the study. Informed consent and a baseline evaluation including laboratory testing were performed prior to surgery.
Investigators performed the spinal surgical 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.
Subjects who met all the inclusion criteria and had either a spontaneous CSF leak, or leak upon Valsalva maneuver at 20-25 cm H_2O for 5-10 seconds, were randomized intraoperatively (2:1) to either Spinal Sealant or control, stratified by site in blocks of 6. Up to two applications of the assigned treatment were allowed. Control, i.e., standard of care, treatment was defined as treatment of the dural repair with up to 2 attempts at standard of care methods ((i.e., devices designed to provide an intra-operative watertight closure). **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.**

Key Pre-operative Inclusion criteria:

1) Age 18-75 years
2) Scheduled for spinal surgery with dural incision.
3) Procedure is planned to be CDC Class I/Clean.

Key Pre-operative Exclusion Criteria

1) Active spinal or systemic infection
2) Patient will require additional spinal surgery within the planned study duration
3) Chronic steroid therapy unless discontinued at least 6 weeks prior surgery (chronic defined as 4 weeks or greater of treatment)
4) Diagnosed and documented compromised immune system or autoimmune disease.
5) Had chemotherapy treatment within 6 months prior to, or planned during the study follow-up period.
6) Prior radiation therapy to the surgical site or planned radiation within 30 days of surgery.
7) Known malignancy or other condition with a prognosis of less than 6 months.
8) Documented history of uncontrolled diabetes.

Intra-operative Inclusion Criterion

1) Presence of a non-watertight closure*, either spontaneous or after Valsalva maneuver to 20-25cm H_2O for 5-10 seconds.

*** Definition of a non-watertight closure: any overt flow, seepage, weeping, or sweating of CSF through the dura, regardless of volume.**

Intra-operative Exclusion Criteria

1) Patient requires synthetic or non-autologous duraplasty material.
2) Patient has a gap of greater than 2mm remaining after primary closure.

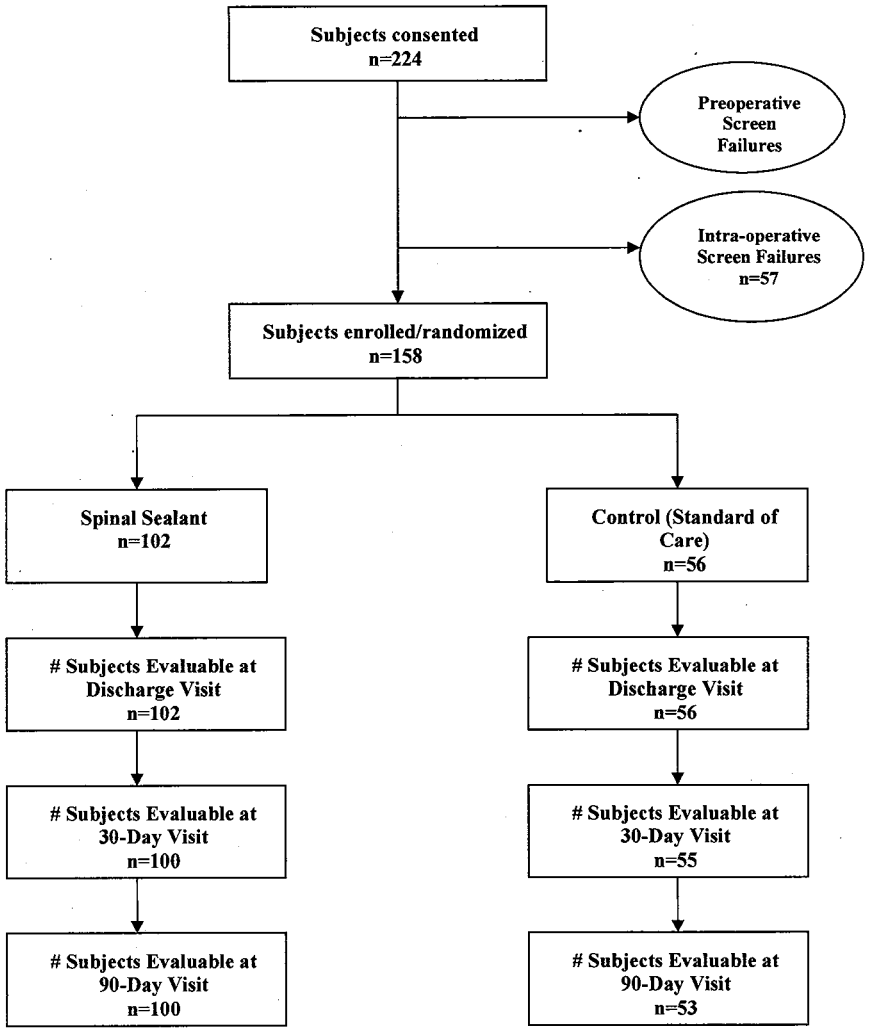
Subjects scheduled for an elective spinal procedure requiring a dural incision were considered for study participation. Enrollment included, but was not limited to, the following surgical procedures:

- Intradural tumor removal (cervical, thoracic, lumbar, sacral).
- Chiari Malformation procedures entailing a dural incision at or below the C1 level.
- Intradural arteriovenous malformation (cervical, thoracic, lumbar).
- Release of tethered cord (lumbar).
- Syringomyelia surgical intervention (cervical, thoracic, lumbar).

Randomization and screening:

Prior to the initiation of the study, a treatment randomization scheme was generated and randomization envelopes were provided to each investigational site. The study was initiated with a 1:1 randomization scheme, which was updated to a 2:1 scheme (Spinal Sealant: Control) when Revision B of the investigational clinical protocol was implemented. The majority (>90%) of study subjects were randomized under protocol Revision B. In Revision B, subjects who met all the inclusion criteria and had either a spontaneous CSF leak, or leak upon Valsalva maneuver at 20-25 cm H_2O for 5-10 seconds, were randomized intraoperatively (2:1) to either Spinal Sealant or control, stratified by site in blocks of 6. Treatment assignments were placed into sealed envelopes, thus blinding the surgeon to treatment assignment prior to randomization. Once the dural closure was completed and the subject was confirmed to meet all intra-operative eligibility criteria, the randomization envelope was opened disclosing the treatment assignment to either Spinal Sealant or Control. All randomized subjects were blinded until they completed the 90 day end of study visit. Two hundred twenty-four patients were consented prior to surgery. Nine patients were preoperative screen failures and 57 patients were intraoperative screen failures (most not leaking). Therefore, 158 patients were actually enrolled and randomized. Of the 158 patients, 102 were treated with DuraSeal and 56 were treated with SOC. These patients composed the Intent-To-Treat (ITT) population. The per-protocol population consisted of 155 patients (102 DuraSeal, 53 SOC), where 3 control patients were excluded because the investigator did not use the protocol SOC methods. An intraoperative randomization was necessary to to ensure there was no bias when completing the primary dural closure and to preserve the 2:1 balance between treatment groups. The randomization occurred after the investigator evaluated the presence of a baseline leak. The investigator was not blinded during leakage assessment after primary treatment., a potential source of bias.

Subject Course of Treatment and Follow-Up



Among the 66 subjects that were not randomized, 9 were determined to be pre-operative screening failures, failing to meet the pre-operative eligibility criteria after providing informed consent. If there was an incidental finding of any preoperative exclusion criteria during the operative procedure the subject was considered an intra-operative failure. Fifty-seven (57) of the 66 subjects that were not randomized failed to meet the intra-operative eligibility criterion and were considered intra-operative screening failures. The criteria that excluded these 66 subjects are summarized in Table 7.

The 66 subjects that were consented and subsequently determined to be ineligible (either preoperatively or intra-operatively) were withdrawn from the study and not followed.

Table 7. Reasons for Preoperative/Intra-operative Screening Failures – Summary

[illegible]	[illegible]
Preoperative Criteria	
Subject is not between 18 and 75 years of age	1 (1.5)
Subject is not scheduled for a spinal procedure that entails a dural incision	2 (3.0)
Subject will require additional spine surgery within the study time period	1 (1.5)
Subject has had previous spinal surgery involving dural exposure and/or entry at the same level(s) as the study procedure	1 (1.5)
Subject has been treated with chronic steroid therapy unless discontinued more than 6 weeks prior to surgery (standard peri-operative steroid are permitted)	1 (1.5)
Subject has documented history of significant coagulopathy with a PTT>35 sec, PT/INR > 1.2, receiving aspirin or NSAIDS at the time of surgery	1 (1.5)
Subject has a documented history of uncontrolled diabetes	1 (1.5)
The investigator determines that the subjects should not be included in the study for reason(s) not already specified	6 (9.1)
Intra-Operative Criteria	
There is no presence of non-watertight closure, either spontaneously or upon Valsalva maneuver at 20-25cm H20	48 (72.7)
Incidental finding of any of the preoperative exclusion criteria	11 (16.7)
Subject requires use of synthetic or non-autologous duraplasty material	12 (18.2)
Subject has a gap of > 2mm remaining after primary closure	3 (4.5)
Subject has undergone a Chiari malformation procedure that does not entail a dural incision at or below the C1 level	3 (4.5)
Investigator determines that participation in the study may jeopardize the safety or welfare of the patient	7 (10.6)
Subject has undergone a syringomyelia procedure in which the shunt is not placed in the subarachnoid position	1 (1.5)

Note: Percentages are based on the number of patients who were consented but not randomized.
Note: Patients may fail more than one criterion so percentages may add to more than 100%.

From the protocol regarding both treatment and control groups:

3.4.4 Procedure

The investigator will conduct the spinal procedure according to the appropriate standard procedures and practices at his/her institution. The sutured dural repair will be completed to the investigator's satisfaction. Autologous duraplasty materials (i.e., fascia, fat, pericranium, or muscle) may be used as necessary. The use of synthetic, non-autologous dural substitutes, and/or blood-based sealants is not permitted.

Upon satisfactory completion of the sutured dural repair, the patient will be evaluated to confirm eligibility. The dural repair will be evaluated for the presence or absence of a watertight closure with a baseline Valsalva maneuver at 20-25 cm H_20 for 5-10 seconds. If there is a spontaneous expression of CSF, no Valsalva maneuver is required. The type (i.e. overt versus seepage of CSF around the suture points) and nature of the non-watertight closure (i.e., spontaneous versus upon Valsalva) will be recorded. If the patient meets all the intra-operative eligibility criteria, the patient will be randomized to either the Spinal Sealant arm or the control arm. Randomization will be based

Control treatment

Control treatment is defined as: treatment of the dural repair with up to 2 attempts at standard of care methods ((i.e., devices designed to provide an intra-operative watertight closure).

If the patient is randomized to the control arm: **one additional attempt to obtain watertight closure with additional sutures (and the use of autologous duraplasty material as needed) is permitted. A subsequent Valsalva maneuver at 20-25 cm H_2O for 5-10 seconds (if there is a spontaneous expression of CSF, no Valsalva maneuver is required) will be performed. If the dural closure is not watertight after the second suture attempt, the "control" will be considered a failure and conventional management of non-watertight closure will be considered, at the discretion of the investigator. All procedural information will be recorded on the case report forms.**

Treatment

Prior to initiation of enrollment, all study surgeons were trained on the proper use of the DuraSeal Spine Sealant System. Patients who were scheduled for an elective spinal procedure that required a dural incision and who met pre-operative study eligibility criteria were invited to participate in the study. Informed consent and a baseline evaluation including laboratory testing were performed prior to surgery. The investigator performed the spinal procedure and sutured dural repair according to the standard procedures and practices at his/her institution. Autologous duraplasty materials (i.e., fascia, fat, pericranium, or muscle) were used as necessary to augment dural closure. Following primary dural closure, the subject was evaluated to confirm intra-operative eligibility. The dural repair was evaluated for the presence or absence of watertight closure with a baseline Valsalva maneuver at 20-25 cm H_20 for 5-10 seconds. If there was a spontaneous expression of CSF, no Valsalva maneuver was required. The type (e.g, overt versus seepage of CSF around the suture points) and the nature of the non-watertight closure (i.e., spontaneous versus upon Valsalva) was recorded. If non-watertight closure was present, the subject was randomized to either DuraSeal Spine Sealant or Control. Randomization was based on an approximately 2:1 (Sealant: Control) ratio. Randomization was considered the point of enrollment; therefore, subjects that did not meet the intra-operative eligibility criteria were withdrawn from the study without additional follow-up. Following treatment of the dural incision with either the DuraSeal Spine Sealant or chosen Standard of Care methods, subjects were assessed for the primary efficacy endpoint, defined as a watertight closure of the dural repair intra-operatively, confirmed by Valsalva maneuver at 20-25 cm H_20 for 5-10 seconds. Following surgery, subjects were seen at the following time points:

- Discharge (within 7 days post-operative, but prior to hospital discharge)
- 30 Day post-operative visit (-7 days/+ 14 days)
- 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.

The following information was documented on case report forms:

- ASA Score
- Duration of surgery
- Type of procedure, e.g., tumor removal
- Location and approach of spinal procedure, e.g., target levels
- Linear extent of dural incision
- Any autologous duraplasty materials used
- Randomization assignment
- Baseline and post-treatment Valsalva maneuver pressures
- Evaluation of non-watertight closure: size and nature
- Use of shunts/drains
- Sealant application information, if applicable, e.g., lot number, volume, number of applications, time of application(s) and ease of use
- Sutured repair (control) information, if applicable, e.g., number of suture attempts, time of suture attempts
- Any further adjunctive therapy to obtain watertight closure
- Intra-operative adverse events (occurring after randomization)
- Prophylactic antibiotic and anti-inflammatory regimens
- Estimated blood loss

The patients were monitored for post-procedure CSF leakage through study completion. Management of any CSF leak was left up to the physician's discretion. All management treatments were documented.

Primary effectiveness endpoint

The primary efficacy endpoint was the percent success in obtaining a watertight closure following assigned treatment (Spinal Sealant or Control) where success is defined as:

- A watertight closure of the dural repair intra-operatively after assigned treatment, confirmed by Valsalva maneuver at 20-25 cm H_2O for 5-10 seconds.

This was a superiority study. The success rates for the Spinal Sealant group and the control group were compared. The null hypothesis for this study was that the success rate (Ps) for the Spinal Sealant group was not higher than the success rate (Pc) for the control group (Ps < PC). The alternate hypothesis was that the success rate for the Spinal Sealant group was higher than the success rate for the control group (Ps > PC). The sponsor's criterion for superiority was based on a rather large difference (35 percentage points) between the two treatment groups: 85% success rate for Sealant vs, 50% success rate for the control. A difference of this size could be seen with 32 patients per group with 80% power. However, it was determined that at least 100 Spinal Sealant patients should be assessed for the safety profile. Therefore, a 2:1 randomization schemed with 100 Sealant and 50 control patients, with inflation for possible 5% loss to follow-up for the later follow-ups, was deemed appropriate. The sample size was certainly adequate for effectiveness (being highly significant), but note that rare complications could not have been seen in a sample of 100.

Safety evaluations

Summary data was presented on the following:

- Presence or absence of CSF leaks within 90 days post-procedure 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 as determined from clinical diagnosis based on the CDC definitions of surgical site infection
- Adverse events
- Laboratory testing: hematology (CBC, including WBC, RBC, Hct, Hgb, platelet count (excluding differentials), electrolytes (Na, K, Cl, CO_2), renal function (BUN, creatinine), liver function (ALP, ALB, total bilirubin, ALT, AST) and glucose; serum or urine pregnancy tests
- Neurological assessment: including cranial nerve, neurological, motor, sensory, reflex, gait, and symptoms of nerve root compression
- Wound healing assessment

From the protocol:

3.4 Study Procedures and Data Collection

3.4.1 Study Schematics

The schematic of the trial is presented below.

	Pre-Op. Baseline Visit (Within 14 days)	Procedure	Discharge Visit (Within 7 Days Post-procedure, prior to discharge)	30 Day Post-procedure Visit (-7 days/+ 14 days)	90 Day Post-procedure Visit (± 14 days)
Informed Consent	X				
Medical/ Surgical History	X				
Current Status/ Physical Exam	X		X	X	X
Vitals	X		X	X	X
Neurological Exams	X		X	X	X
Laboratory Tests [a]	X [b]		X [c]	X	X
SF-12v2 / VAS	X			X	X
Dural Closure		X			
Evaluation(s) for Watertight Closure		X	X	X	X
Randomization and Assigned Treatment		X			
Wound Healing Assessment			X	X	X
Length of Hospital Stay			X		
Peri-Operative Prophylactic Medications [d]		X			
Adverse Events		X	X	X	X

[a] Hematology plus Platelets (excluding differentials), Electrolytes (Na, K, Cl, CO_2), Renal Function (BUN, Creatinine), Liver Function (ALP, Total Bilirubin, ALT, AST), and Glucose.
[b] For the baseline visit, the following will also be collected: ALB and serum or urine pregnancy test for females of childbearing potential.
[c] For the discharge visit, electrolytes (Na, K, Cl, CO_2) and Glucose will not be collected.
[d] The following intra-operative medications will be recorded on the case report forms: prophylactic antibiotic regimen and anti-inflammatory regimens.

Statistical Plan

Using a two-tailed continuity corrected χ^2 test and a level of 0.05 and a power of 80%, assuming a primary endpoint success rate for Spinal Sealant of 85% and a primary endpoint success rate for control of 50%, the required sample size is 33 patients for each treatment group, or a total of 66 patients. However, for purposes of safety assessment, a minimum of 100 patients is necessary to complete the study. With an assumed dropout rate of 5%, 105 patients were to be treated in order to

obtain 100 completed patients. As noted under the section on randomization and screening, the original proposed protocol included a 1:1 randomization of 50 and 50 patients. However, this was revised to a 2:1 randomization with 100 patients treated with the investigative device. Subsequently, the statistical analysis was changed to a two-sided Fisher's Exact Test, testing for a difference in success rates between treatments. FDA approved the change to using the Fisher's Exact test for the primary endpoint.

All statistical tests were two-sided at the 5% significance level, unless otherwise indicated. Data collected in this study are presented using summary tables and subject data listings. Summary tables are presented by treatment group (Spinal Sealant and Control). Continuous variables are summarized using descriptive statistics, specifically the mean, median, standard deviation, standard error, minimum and maximum. Categorical variables are summarized by frequencies and percentages. Statistical analyses were performed and tables and listings produced using SAS® Version 9.1 or higher.

Primary Efficacy Analysis

The efficacy analyses were performed on the ITT population. The primary efficacy analysis as noted, was performed using Fisher's Exact Test to test for a difference in success rates in obtaining a watertight closure between treatment groups. Additionally, a 95% CI for the success rate was computed for each treatment group. A logistic regression analysis was performed for the primary efficacy endpoint with terms for treatment group, investigative site and the treatment by site interaction. If the interaction term was statistically significant ($p < 0.10$), results for the primary efficacy endpoint were presented by site as well as overall. These analyses were repeated comparing the Spinal Sealant group to subgroups of the Control group defined by the material used (sutures, adhesive/glue, soft tissue patch/vascular graft, hemostatic agent, other).

Safety Analyses

Summary results are presented for the safety population for the presence or absence of endpoint CSF leak within 90 days post-procedure and the presence or absence of surgical site infection within 90 days postprocedure. Fisher's Exact Test was used to test for a difference in the proportions of subjects with CSF leaks and the proportions of subjects with surgical site infection between the two treatment groups.

Time to first endpoint CSF leakage and time to first surgical site infection, each measured in days from the date of surgery, are summarized for each treatment group using the Kaplan-Meier method. For each endpoint, graphs of the Kaplan-Meier estimated survival distributions are presented for each treatment group. The log-rank test was used to test for differences between the treatment groups.

Additionally, the numbers and percentages of subjects experiencing any adverse event (AE), any serious adverse event (SAE), and any device related AE are presented by treatment group, and the percentages were compared using Pearson's chi-square test. The incidence of adverse events is summarized by body system and preferred term, overall, by severity, and by relationship to study device. Body system incidences were compared between treatment groups using Pearson's chi-square test.

Adverse events that are related to the investigational device or Control treatment are summarized. Device related events include events for which the answer to the question "Is this event related to the Investigational Device (Spinal Sealant subjects) or Standard of Care (Control subjects)?" is "Yes". All adverse events are listed.

Descriptive statistics are presented by visit for the actual values, the changes from baseline, and the differences between treatment groups in changes from baseline for all quantitative laboratory tests. A table is presented showing the status (normal; abnormal, clinically significant; abnormal, not clinically significant) at each post-procedure visit for each laboratory parameter collected.

Similarly, descriptive statistics are presented by visit for the actual values, changes from baseline, and the differences between treatment groups in the changes from baseline for the vital signs data. A table is presented

showing the status (normal; abnormal, clinically significant; abnormal, not clinically significant) at each post-procedure visit for each vital sign parameter (blood pressure, heart rate, temperature).

A shift table presents changes in status (normal, abnormal, not done) from the baseline visit to each post-baseline visit for each body system examined in the physical examination. Data from the neurological assessments and the post-procedure wound assessments are summarized by visit for each treatment group.

SF-36 and VAS Pain Scores
Descriptive statistics are presented by visit for the actual values, changes from baseline, and the differences between treatment groups in the changes from baseline in the SF-36 domain and summary scores and the VAS pain score for each treatment group. Frequencies and percentages are presented by treatment group for the SF-36 health transition score.

Analysis by Kit Configuration
All key safety and efficacy analyses were stratified between kit configuration types.
Variables assessed included procedure type, CSF leak rate, surgical site infection rate and neurological complications rate.

Protocol Changes
In summary, there were several changes made to the clinical protocol during the conduct of the study. The major ones included: increasing the sample size from 105 to 158 subjects; modifying the randomization scheme from 1:1 to 2:1; increasing the number of sites from 20 to 25; and adding a second device configuration (5 mL kit) so that surgeons would have a choice. The statistical analysis plan was also modified so that a more conservative two-sided analysis would be used and an analysis stratified by kit configuration was added. These changes were approved by FDA.

Protocol Revision B. Effective September 19. 2005

- Sample size increased from 105 subjects to 158 subjects and the randomization scheme was modified from 1:1 to 2:1, based on written correspondence from the FDA that 100 Spinal Sealant subjects would be required to adequately characterize the device safety profile.

- The number of investigational sites was increased from 20 to 25.

- A second device configuration was included (5 mL Polymer Kit with Dual Liquid Applicator) to allow surgeons flexibility in the selection of application devices for delivery of the Spinal Sealant.

- The visit window for the Baseline visit was extended from 14 to 30 calendar days.

- Inclusion/exclusion criteria: Allowed for inclusion of subjects with syringomyelia (however, subjects with syringomyelia where the shunt is not placed in the subarachnoid position were to be excluded) and modified the intra-operative exclusion criteria to clarify that subjects undergoing Chiari Malformation surgery that does not entail a dural incision at or below the Cl level were to be excluded.

- Modified and added language regarding ultra-operative procedure including use of further adjunctive therapy and wound closure.

Protocol Revision C, Effective June 5, 2006

- The protocol was modified to clarify that subjects must remain blinded until they complete the study.

- Definition of Deep Surgical Site Infection was corrected (had been incorrectly transcribed from the CDC guidelines).

- Definitions for fever clarified to distinguish between elevated temperature (body temperature to between 99.5°F and 100.4°F); fever (above 100.4°F) and high grade fever (above 101.3°F).

In addition to the above noted protocol revisions, supplemental data in addition to requested data on the eCRF was collected for all enrolled subjects including the following: previous spine surgery at any region of the spine and corresponding vertebral levels, radiation to any region of the spine, signs or symptoms of hydrocephalous, tumor size, and post-operative steroid use.

Statistical Plan: Changes to the Planned Statistical Analysis as Defined in the Protocol that are Reflected in the Statistical Analysis Plan (SAP)

A detailed Statistical Analysis Plan (SAP) was developed in consult with an independent statistician. The SAP pre-identified the analyses to be performed. The SAP was signed by Sponsor management prior to execution of the analysis. In development of the SAP, it became necessary to revise some of the methods identified in statistical section of the clinical study protocol. These changes are summarized below.

- Statistical comparison of primary efficacy endpoint success rates has been performed using a two-sided test as opposed to the one-sided test indicated in the protocol.

- The primary endpoint, the success rate in obtaining a watertight closure, was added to the list of key efficacy and safety variables mentioned in the protocol that are to be analyzed with stratification by kit configuration type. Analogous analyses of the key efficacy and safety variables with stratification by actual total volume used and by normalized total volume used were also added.

- The protocol states that clinical laboratory data will be summarized for each treatment group and laboratory parameter by shifts in status (normal; abnormal, clinically significant; abnormal, not clinically significant) from baseline to post-baseline time points. However, status data is not collected at the baseline visit. Therefore, clinical laboratory data status will be summarized for each post-procedure visit only.

Changes to the Planned Statistical Analysis Plan as defined in the SAP

Following development of the SAP, several changes were instituted following the initial evaluation of the data. These changes are summarized below:

- In the SAP, it was stated that a supplemental table summarizing adverse events that are device related would be included in the analysis. As only one event was noted as device related, a summary table presenting only device related adverse events is not included in this report.

- A supplemental analysis plan was also implemented to analyze additional data that were collected on the safety population.

- A Per Protocol Analysis was added to the analyses, to exclude 3 Control subjects for whom the treating investigator, in violation of the study, chose not to use any protocol specified standard of care methods to achieve a watertight dural closure.

- For comparison between groups of the incidence rates of AEs by body system and of the incidence of device related AEs, statistical testing was performed using Fisher's Exact test rather than Pearson's Chi-Squared test due to small counts.

- In the ITT analysis, the primary efficacy endpoint for [redacted] was imputed as a failure. This is 1 of 3 Control subjects that no Standard of Care method was attempted. For subject safety reasons, the treating investigator did not make an attempt at Standard of Care treatment, per protocol requirements. Due to the fact that after the baseline Valsalva was completed and no further measures were taken to achieve watertight closure, the Valsalva was not repeated. The subject was considered a primary endpoint failure and further adjunctive therapy was applied.

Results

Patient demographics

The baseline demographic characteristics, which included age, gender, height, weight, BMI, smoking status, ASA score, and medical history including previous surgeries were equivalent between treatment groups. The sponsor also reported the breakdown for each treatment group for the type of procedure and the neurological procedural characteristics. Although there were no statistical tests performed on these side by side comparisons, the percentages are similar and there is no indication of any imbalance of baseline demographic or procedural characteristics. Table 7 summarizes the baseline demographic information for the ITT population. Overall the Spinal Sealant group and the Control group are comparable with regards to baseline characteristics. The mean age is similar, at 47.7 years (Spinal Sealant) and 42.3 years (Control). Gender was fairly evenly distributed in this study with approximately 53% female subjects in both treatment groups. A similar percentage of subjects in the Spinal Sealant group (18.6%) versus those in the Control group (16.1%) are current smokers. The mean BMI in the Spinal Sealant group is 27.8 kg/m^2 (Range: 17.9 – 46.2 kg/m^2), similar to the Control group at 29 kg/m^2 (Range: 16.0 – 64.0 kg/m^2). The majority of subjects in both groups have an ASA Score of I or II, indicating most subjects are healthy or presented with only mild systemic disease at the time of the study procedure. The proportion of subjects with an ASA score of III or more, indicating more severe systemic disease was comparable between the two treatment groups, specifically 22.6 % and 21.4% for the Spinal Sealant and Control groups respectively.

Table 8. Baseline Characteristics

Characteristics	Spinal Sealant (N=102)	Control (N=56)
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/m2)		
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)

Patient Medical History

Past and current medical conditions were recorded by body system. No major differences in current medical history were observed between the two groups. The most frequently occurring disease groups were Musculoskeletal Disease and Central Nervous System Disease, both of which had comparable frequencies between the study groups. A summary of current medical history for both treatment groups is provided in Table 9.

Table 9: Current Medical History

System	Spinal Sealant (N=102) n (%)	Control (N=56) n (%)
No Medical History	0 (0.0)	0 (0.0)
CNS Disease	71 (69.6)	40 (71.4)
EENT Disease	24 (23.5)	12 (21.4)
Cardiovascular Disease	48 (47.1)	17 (30.4)
Respiratory Disease	21 (20.6)	12 (21.4)
Dermatology Disease	7 (6.9)	1 (1.8)
Gastrointestinal Disease	39 (38.2)	19 (33.9)
Endocrine Disease	22 (21.6)	12(21.4)
Allergies	36 (35.3)	14 (25.0)
Musculoskeletal Disease	69 (67.6)	32 (57.1)
Genitourinary Disease	26 (25.5)	13 (23.2)
Other	48 (47.1)	20 (35.7)

Note: A subject may have medical conditions in more than one body system so percentages may add to more than 100%
Note: The "Other" category includes various medical conditions, including anxiety, depression, etc.

Procedural Characteristics

The types of surgical procedures performed in the study are summarized in Table 10. The most common procedures performed were tumor removals (62.7% Spinal Sealant, 62.5% Control) and Chiari Malformation (21.6% Spinal Sealant, 32.1% Control) decompressions.

Table 10. Type of Procedure

Type of Procedure	Spinal Sealant (N=102) n (%)	Control (N=56) n (%)
A-V malformation	0 (0.0)	1 (1.8)
Chiari	22 (21.6)	18 (32.1)
Cyst	8 (7.8)	0 (0.0)
Syringomyelia	4 (3.9)	1 (1.8)
Syringomyelia with arachnoid cyst	1 (1.0)	0 (0.0)
Tethered cord	3 (2.9)	1 (1.8)
Tumor removal	64 (62.7)	35 (62.5)

The neurosurgical procedural characteristics are presented in Table 11. The majority of procedures occurred at the cervical spine region (46.1% Spinal Sealant, 57.1% Control). The Spinal Sealant subjects had more thoracic spine level procedures (38.2% Spinal Sealant, 26.8% Control), and the percentages of lumbar spine procedures were similar between the two groups (24.5% Spinal Sealant, 26.8% Control). All surgical approaches were posterior, with the exception of one subject (21-015) who underwent removal of a cervical tumor located anterior and anterolateral to the spinal cord necessitating an anterior approach.

Table 11. Neurosurgical Procedural Characteristics

[illegible]	[illegible]	[illegible]
Location[1], n (%)		
Cervical	47 (46.1)	32 (57.1)
Thoracic	39 (38.2)	15 (26.8)
Lumbar	25 (24.5)	15 (26.8)
Sacral	9 (8.8)	1 (1.8)
Approach, n (%)		
Anterior	0 (0.0)	1 (1.8)
Posterior	102 (100.0)	55 (98.2)
Duration of Surgery (hrs)		
Mean (SD)	3.9 (1.80)	3.8 (1.31)
Median	3.4	3.6
Range (Min, Max)	(1.3,9.2)	(1.6,6.3)
Length of Durotomy (cm)		
Mean (SD)	5.1 (2.72)	5.3 (2.79)
Median	4.7	5.0
Range (Min, Max)	(1.0,18.0)	(1.6,16.0)
Autologous Duraplasty Materials Used[1], n (%)	31 (30.4)	23 (41.1)
Fascia	11 (10.8)	12 (21.4)
Fat	4 (3.9)	2 (3.6)
Pericranium	13 (12.7)	11 (19.6)
Muscle	5 (4.9)	1 (1.8)
Other	1 (1.0)	0 (0.0)
Further Adjunctive Therapy[1], n (%)	0 (0.0)	19 (33.9)
Adhesive/Glue	0 (0.0)	7 (12.5)
Absorbable Gelatin Sponge	0 (0.0)	5 (8.9)
Dural Substitute	0 (0.0)	1 (1.8)
Dural Graft Matrix	0 (0.0)	7 (12.5)
Hemostatic Agent	0 (0.0)	5 (8.9)
Other	0 (0.0)	3 (5.4)
Wound Closure Materials Used[1], n (%)	39 (38.2)	26 (46.4)
Absorbable Gelatin Sponge	21 (20.6)	12 (21.4)
Hemostatic Agent	25 (24.5)	16 (28.6)
Other	16 (15.7)	10 (17.9)

(1) A subject can have more than one location operated on, more than 1 material or therapy used, so the percentages may sum to more than 100%.

Patient Accounting

Because the primary endpoint was assessed intraoperatively, there was no lost-to-follow-up at this assessment or at hospital discharge. There were 5 subjects, however, who did not complete the 90-day study: 2 sealant and 3 controls. The statistical handling of these patients will be discussed below under "Missing Values".

Protocol Deviations

There many protocol deviations, however, most were due to partial assessments not being done, or not being done in the required time frame (lab tests, blood pressure, temperature). There were 2 instances where the randomization envelope had to be discarded because it was opened before surgery (the next one was used), and one instance where an envelope from the old 1:1 scheme was used instead of the 2:1 scheme. There were 15 deviations from the protocol-specified inclusion/exclusion criteria in 14 subjects. Ten subjects did not have the required eligibility lab tests prior to randomization; 2 had concomitant medications excluded by the protocol; 1 had a history of uncontrolled diabetes and 1 had a synthetic duraplasty used for primary dural closure. The sponsor claims that these subjects are representative of subjects likely to be treated with the Spinal Sealant in normal medical practice and has included them in the safety and ITT populations. There were 12 procedural/device related deviations reported in 12 subjects. Most were minor, however for [redacted] "a commercially available DuraSeal Dural Sealant System (PMA P040034) was used off-label after multiple attempts with the 5 mL study kit configuration were unsuccessful". By "unsuccessful", the sponsor has clarified in Amendment 1 that it was unsuccessful in the "application". [redacted] i.e., this patient had synthetic duraplasty used for primary dural closure, was a significant protocol violation in potential favor of the investigational device. The clinical reviewer did not believe the other protocol violations were of significance. The use of the approved DuraSeal for [redacted] was in, the opinion of the clinical reviewer, due to delivery failure and availability of another investigational kit and not due to device failure.

All subjects except 3 controls were included in the per protocol analysis in spite of all the protocol deviations mentioned above. Thus, what the sponsor is calling "per protocol" is really a "correctly treated" cohort, as the only patients excluded were 3 controls who received an off-protocol or no standard of care. An actual Per-Protocol analysis was not performed because the sponsor did not feel the protocol deviations affected the evaluation of the safety or effectiveness of the device. The ITT analysis was primar

Effectiveness
Table 12

Intent to Treat Population				
Treatment Groups	Number of patients	Number of Successes	Percentage of Successes	95% Confidence Interval
Spinal Sealant	102	102	100.0	96.4, 100.0
Control	56	36	64.3	50.4, 76.6
p-value(1)	<0.001			
Per Protocol Population				
Treatment Groups	Number of patients	Number of Successes	Percentage of Successes	95% Confidence Interval
Spinal Sealant	102	102	100.0	96.4, 100.0
Control	53	36	67.9	53.7, 80.1
p-value(1)	<0.001			

(1) p-value from two-sided Fisher's Exact Test testing for a difference in success rates between treatments.

The above table shows that all 102 sealant patients (100%) were successes compared with 64% of the controls. This difference is highly statistically significant at less than the 0.1% level. Ninety-three of 102 sealant subjects had a watertight closure after one application. Of the nine without watertight closure after one sealant application, 2 had spontaneous leaks and 7 had leakage upon Valsalva. All patients were leak-free after the second application. Within the control group, 35 subjects (62.5%) had a watertight closure upon Valsalva following the first application of SOC. Of the 21 who were leaking, 4 were spontaneous and 16 leaked upon Valsalva. In a protocol deviation, [redacted] no Valsalva was done and no additional treatment was given. Only 4 subjects were given a second SOC treatment, of which, one achieved a watertight closure, thereby achieving an overall success rate of 64%. The sponsor was asked why 16 controls were counted as failures and not given a second application of SOC when the first application failed. The sponsor replied in Amendment 1 that "the specific reason why a second attempt was not made was not collected on the CRF"; however, for three of the 16, the

apparent reason may have been safety. Since the protocol stipulated that any second attempt must use the same method as the first, it is possible the physician would see no point in trying the same thing again. The sponsor clarified that the use of DuraSeal was not permitted at any time on the controls, even after they were declared a failure for the purpose of the analysis. The sponsor was asked to provide a sensitivity analysis counting the 16 intraoperatively leaking patients who did not receive a second SOC attempt as successes. The imputed leak-free rates would then be 100% DuraSeal and 92.9% controls. Although the cohorts are much closer in rate of CSF leak prevention, the results are still statistically significant in favor of the DuraSeal group (p=0.015).

The nature of the non-watertight closure was similar between both groups. Specifically 26.5% (Spinal Sealant) vs. 26.8% (Control) of subjects experienced spontaneous expression of CSF, and 73.5% (Spinal Sealant) vs. 73.2% (Control) experienced a non-watertight closure upon Valsalva following primary dural repair. The type of leak (overt vs. seepage at suture points) was also comparable between the two groups, specifically 12.7% (Spinal Sealant) vs. 7.1% (Control) of subjects experienced an overt leak, and 87.3% (Spinal Sealant) vs. 92.9% (Control) of subjects displayed seepage at suture points.

Among Spinal Sealant subjects, the mean number of kits used was 1.4 overall including 2 mL and 5 mL kits (Table 13). The mean total volume of Spinal Sealant used on the first application was 2.9 mL. Among those subjects that required a second application, the mean volume of Spinal Sealant used was 2.9 mL with volumes ranging from 0.6 to 5.0 mL.

Table 13. Spinal Sealant Application Characteristics

	Parameter	Spinal Sealant (N=102)
Number of Spinal Sealant Applications per Patient		
1	n(%)	93 (91.2)
2	n(%)	9 (8.8)
Total Volume of Spinal Sealant Used - First Application (mL)	n	102
	Mean	2.9
	Median	2.0
	SD	1.73
	SE	0.17
	Minimum - Maximum	0.5-8.0
Total Volume of Spinal Sealant Used - Second Application (mL)	n	9
	Mean	2.9
	Median	2.5
	SD	1.73
	SE	0.58
	Minimum - Maximum	0.6-5.0

Two applications of a standard of care material (Table 14) were required in 4 (7.1%) of Control subjects. Three Control subjects received no SOC attempts and therefore represented protocol deviations. These subjects have

been excluded in the PP efficacy analysis. Sutures (44.6%) and fibrin glue (51.8%) were commonly selected as a standard of care method at the first attempt.

Table 14. Control Application Characteristics

[redacted]	[redacted]
Number of Control Applications	
0	3 (5.4)
1	53 (94.6)
2	4 (7.1)
Materials Used for Control - First Application	
Sutures	25 (44.6)
Adhesive/Glue	29 (51.8)
Soft Tissue Patch/ Vascular Graft	4 (7.1)
Hemostatic Agent*	7 (12.5)
Other	1 (1.8)
Materials Used for Control - Second Application	
Sutures	3 (5.4)
Adhesive/Glue	1 (1.8)

* Upon sponsor re-review of the medical records and provided to FDA in a PMA Amendment it was determined that in a majority of subjects (5/7) where the CRF stated a hemostatic agent was used as a SOC material for dural closure, it was truly used to close the wound (muscle, soft tissue) after the dural closure was already complete. The study protocol allowed the investigator to close the wound per standard practice, therefore allowing the use of hemostatic agents for wound closure was permitted. In two [redacted] hemostatic agents were used as a SOC treatment for dural closure, in deviation to the protocol.

A logistic regression analysis of treatment group, investigative site, and treatment by site interaction was performed but because all of the sealant subjects were successes, there could be no interactions or significant covariates related to efficacy. The sponsor also did analyses to show that neither configuration of kit used nor volume of sealant applied was related to presence of CSF leak within 90 days, surgical site infection (SSI) within 90 days, or neurological complications.

Missing values

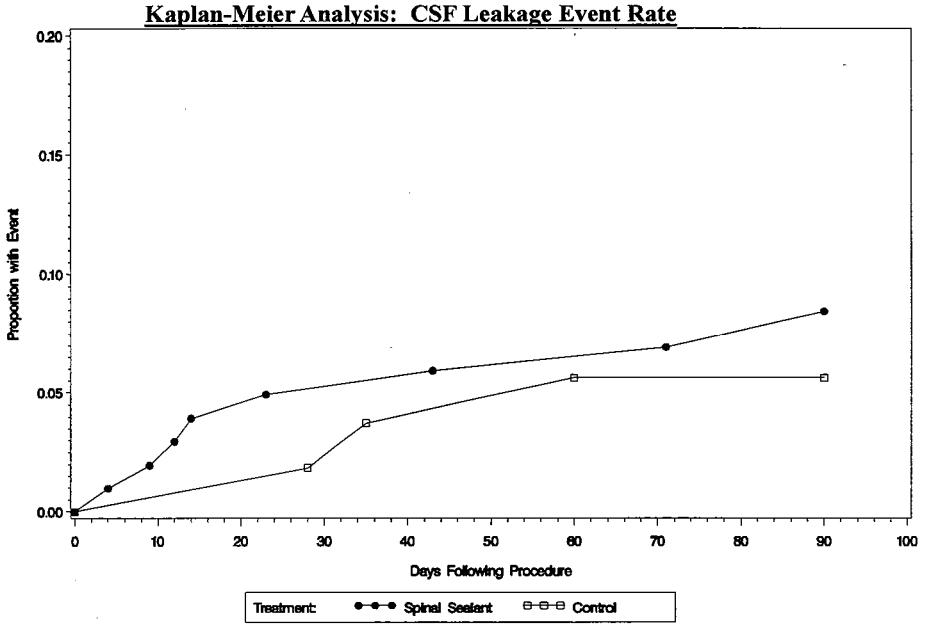
As far as the intraoperative primary endpoint is concerned, everyone was present and there was no need for imputation of missing values for the ITT analysis. For post-operative leaks, two sealant subjects and 3 controls did not have a 90 day follow-up. The sponsor was asked to perform a sensitivity analysis where all missing were counted as failures and a worst case analysis where the missing DuraSeal were failures and the missing controls were successes. The sponsor did this and there was no change in conclusion.

Safety:

Safety of the 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 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. The incidence of post-operative leaks through day 90, based on 102 sealant and 56 controls, was 7.8% in the sealant group vs. 5.4% in the control (p=0.748, Fisher's Exact test). The Kaplan-Meier estimates, which include the 5 incomplete subjects only for the length of time they were followed, were 8.4% sealant vs. 5.6% control (p=0.578).

Kaplan-Meier Analysis: CSF Leakage Event Rate

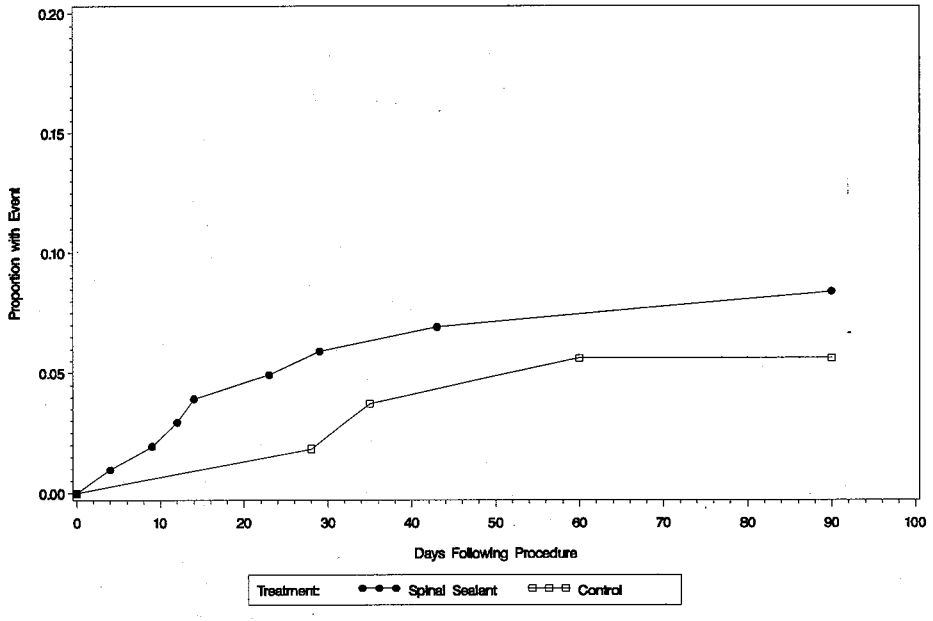


Source: Table 7.1.2

Program Name: C:\CONFLUENT\DRS05_001\DRS\FIGURES\F01RTF.SAS Creation Date, Time: 09APR08 09:41

Upon sponsor re-review of DuraSeal Spine Sealant Clinical Study Report DRS-05-001 [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, the updated Kaplan-Meier Analysis is below.

Sponsor Updated Kaplan-Meier Analysis: CSF Leakage Event



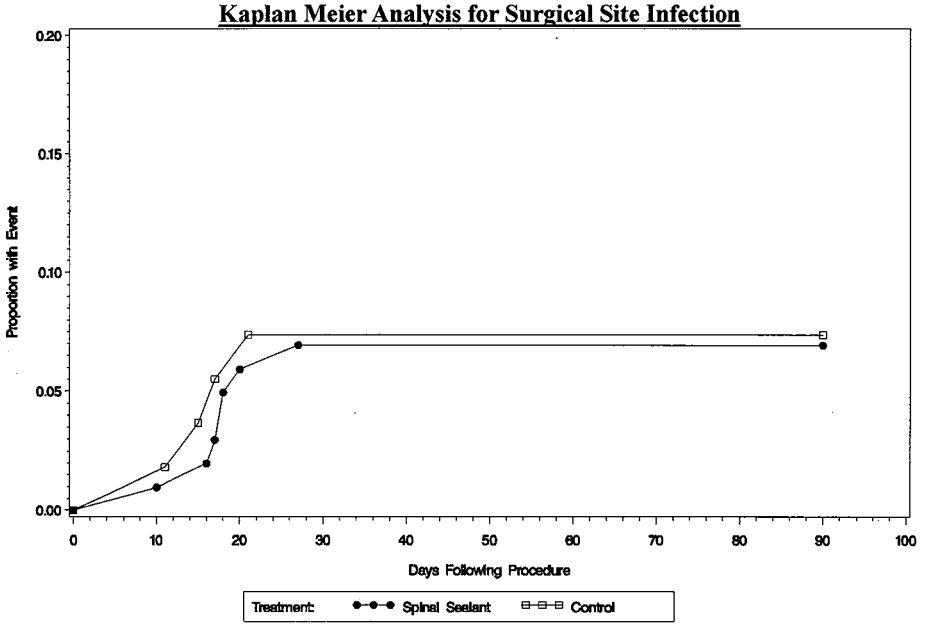
Source: Table 7.1.2

Program Name: C:\CONFLUENT\DRS05_001\DRS\FIGURES\F01RTFIM.SAS Creation Date, Time: 18MAR09 10:10

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

The incidence of overall post-operative surgical site infections was also comparable (6.9% sealant vs. 7.1% control, p= 1.00). An additional Kaplan-Meier analysis of time to onset of SSI was also not significant (p=0.90, log-rank test).

Kaplan Meier Analysis for Surgical Site Infection



Source: Table 7.2.2

Program Name: C:\CONFLUENT\DRS05_001\DRS\FIGURES\F02RTF.SAS Creation Date, Time: 09APR06 09:41

A potentially important observation was that there were 5 deep surgical site infections (SSI) in the sealant group as opposed to only 1 in the control. The sponsor maintains that 2 of these deep SSI's were among sealant patients who were erroneously enrolled in the trial (uncontrolled diabetes and revision surgery). Also, there were 5 subjects in the sealant group that experienced a serious neurological deficit as compared to one in the control group. There were no clinically relevant differences in safety outcomes between the 2 groups with respect to laboratory evaluations, vital signs, physical exam, and wound healing. By Day 30, 96% of the sealant group and 94.5% of the controls were considered by the examiner to have a well-healed wound.

Adverse Events, Serious Adverse Events and Device Related Adverse Events

Table 15 provides an overview of the incidence of adverse events by category. Overall, 93.1% of subjects within the Spinal Sealant group and 91.1% within the Control group experienced at least one AE, and 29.4 % and 17.9% of subjects within the Spinal Sealant and Control groups, respectively, experienced at least one SAE. The high adverse event rate within both groups is a reflection of the fact that a very conservative approach was used in the capture and monitoring of adverse events and is also consistent with a subject population undergoing serious and invasive neurological procedures. There were no unanticipated adverse device effects noted for either treatment group and only one subject within the Spinal Sealant group (1.0%) was noted to have a device-related event as determined by the investigator.

Table 15: Summary of Adverse Events (AEs) and Serious Adverse Events (SAEs)

[illegible]	[illegible]	[illegible]	[illegible]
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
Number of Subjects (%) With At Least One Device-Related AE	1 (1.0)	0 (0.0)	0.646

(1) p-value from Pearson's chi-square test or Fisher's exact test for a difference between treatment groups in the percentages of patients experiencing at least one AE in that given category as appropriate.

Discussion

Review of the study design and results raised questions and concerns for FDA reviewers. The following issues were identified and additional information was requested by FDA of the sponsor to address them:

- How were control (SOC) measures employed?
- Primary endpoint – why should it be considered clinically relevant when it did not correlate with a reduced CSF leak rate at 3 months, follow-up? What information might explain the 3 month treatment group CSF leak rate?
- AE rates – is the higher rate of adverse events in the treated group clinically significant, and/or device-related?

How were control (SOC) measures employed?

The clinical reviewer felt that the "standard of care" methods were used on the control group were unclear. Several methods were mentioned as examples, and sometimes multiple methods were used simultaneously. The sponsor states that "sutures, application of adhesives/glues such as fibrin glue, and application of soft tissue/vascular graft patching" are considered SOC options. FDA requested a listing of each SOC technique used in the control group. The information was provided and is summarized as follows:

- 56 patients treated in the SOC group
- First attempt at SOC treatment: 28 adhesive glue, 25 suture, 2 graft, 2 hemostatic agent, 1 other [redacted]
- Result after first treatment: 36 successes (64%), 20 failures (36%)
- Patients who had a second SOC attempt: 4 patients (1 adhesive glue, 3 suture)

Only SOC methods designed to "provide a watertight closure" were allowed prior to declaring the patient a success or an intra-operative failure. The acceptable SOC techniques to use were adhesive glue, additional sutures, or autologous graft (muscle/fascia), and excluded DuraGen and Gelfoam. The sponsor also clarified that "the choice of 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." FDA considers the study design flawed in that the investigator had to use the same SOC technique in the second attempt. For instance, if the surgeon attempted to over-sew the dural incision without success, they should have been allowed to apply adhesive glue as the second attempt. FDA believes that this may have biased the study, in terms of the primary efficacy endpoint, in favor of DuraSeal. The enforced use of the same SOC method on a second attempt also possibly clarifies why only 4 patients went on to a second SOC attempt, i.e., because the investigator thought that it would be unsuccessful given the failure of the first attempt. However, given the fact

that DuraSeal achieved 100% intra-operative success, this still would not have changed the overall study result in terms of the primary endpoint.

In response to FDA's request for an explanation as to why 16 patients were considered failures without a second SOC treatment, the sponsor reiterated that surgeons were not required to make a second attempt and that any second attempt had to employ the same SOC technique as the first. FDA believes that the percentage of Control patients with an intra-operative leak would have been substantially lowered by permitting cross-over between, for example, sutures and fibrin glue as is done in clinical practice. FDA then requested that the 16 patients who did not undergo a second SOC treatment be considered as successes of the primary endpoint, and asked that a statistical analysis be performed. The analysis resulted in a 92.9% (52/56) success rate in the control group. Compared to 100% in the DuraSeal group, there was still a statistically significant difference between study groups (p= 0.015).

The panel will be asked to address the clinical validity of the Primary endpoint. Why should the Primary endpoint be considered clinically relevant when it did not correlate with a reduced CSF leak rate at 3 months, follow-up? What information might explain the 3 month treatment group CSF leak rate?

The results observed for the intra-operative CSF leak assessment indicate that the device worked completely effectively, yet the treated and control cohorts had equivalent CSF leak rates at 90 days. Therefore, the study does not demonstrate a relationship for prevention of an intra-operative dural leak leading to prevention of a post-operative (clinically meaningful) CSF leak manifest as either an incisional CSF leak or a pseudomeningocele. Furthermore, the design of the study required attempted closure prior to randomization. This likely negatively affected the control group. This affect would be due to the initial attempts at closure without additional materials which would be expected to fail in a significant portion of spinal cases, particularly the surgeries for Chiari malformation (though this could be overcome with appropriate use of autologous tissue). Statistically, the treatment difference in favor of DuraSeal was marked and robust, meaning that sensitivity analyses on the protocol deviations and missing data did not change the conclusion. That said, the clinical utility of the timing of the primary endpoint (intraoperative as opposed some post-operative timepoint) should be assessed. There was no statistical difference in post-operative leaks through 90 days, although the sealant group did slightly numerically worse, but this could have been due to chance.

In order to understand why patients who had achieved DuraSeal-mediated watertight closure, with comparison to control cohort CSF leakers, FDA requested a comprehensive analysis of patients who leaked in both groups taking into account the following factors:

- Type of procedure, location of surgery, length of dural opening
- Timing of treatment failure, CSF leak through the skin vs. pseudomeningocele, correlation to SSI or meningitis, need for re-operation
- Significant co-morbidities that might limit wound healing
- Details of skin closure technique and post-operative activity limitations
- The SOC technique used in each control case

Information for all leakers in both cohorts was provided. There were 8 leakers in the DuraSeal group and 3 leakers in the SOC group with details as follows:

- Type of procedure:
  - DuraSeal: 3 Chiari malformation (3/22 = 13.6%), 3 tumor removal (3/64 = 4.6%), 1 tethered cord (1/3 = 33.3%), 1 syringomyelia (1/5 = 20%)
  - SOC: 2 tumor removal (2/3), 1 tethered cord (1/3)
- Location of surgery:
  - DuraSeal: 6 posterior cervical (4 craniocervical junction), 2 lumbosacral
  - SOC: 2 posterior cervical (2 craniocervical junction), 1 lumbosacral

- Length of dural opening:
  - DuraSeal: 2-10 cm (mean 4.7cm)
  - SOC: 2.5-4 cm (mean 3.2 cm)
- Timing of treatment failure:
  - DuraSeal: 3-70 days (mean 27.2 days)
  - SOC: 27-59 days (mean 42 days)
- CSF leak through the skin vs. pseudomeningocele:
  - DuraSeal: 5 pseudomeningocele, 3 fistula
  - SOC: 0 through the skin, 3 pseudomeningocele
- Correlation with SSI/meningitis:
  - DuraSeal: no mention of infectious complications in "CSF leak details"
  - SOC: no mention of infectious complications in "CSF leak details," however in question 1c. the patient who leaked at 27 days was noted to have developed a deep SSI and bacterial meningitis
- Need for re-operation:
  - DuraSeal: 5 re-operations, 1 aspiration of pseudomeningocele, 1 lumbar drain, 1 unknown
  - SOC: 1 re-operation, 1 aspiration of pseudomeningocele, 1 lumbar drain
- Co-morbidities that might limit wound healing:
  - DuraSeal: 1 hydrocephalus; 0 prior radiation to the spine (1 unknown)
  - SOC: 1 hydrocephalus; 0 prior radiation to the spine (1 unknown)
- Details of skin closure techniques:
  - DuraSeal: deep tissues were closed in layers with absorbable sutures in each case; running nylon suture was used for the skin in 6 cases, staples in 1, and unknown in 1 case
  - SOC: deep tissues were closed in layers with absorbable sutures in each case; running nylon suture was used for the skin in 2 cases with 1 unknown
- Time to first activity post-op:
  - DuraSeal: 1-4 days (mean 2.4 days) with 3 unknowns
  - SOC: 1-3 days (mean 2 days)

The following differences in the patients who leaked were noted: 3 Chiari decompressions leaked in the DuraSeal group (3/22 = 13.6%) vs. 0 in the SOC group, there were 6 early leakers (3, 8, 13, 22, 27, and 29 days) in the DuraSeal group whereas the earliest leak in the SOC group was 27 days, there were 5 CSF leaks through the skin in the DuraSeal group vs. 0 in the SOC group, and there were 5 patients in the DuraSeal group who went on to re-operation compared to 1 in the SOC group. In analyzing these differences, the CSF dynamics at the craniocervical junction can put any dural repair at risk of failure. While 3 Chiari decompressions leaked in the DuraSeal group compared to 0 in the control, one must also consider that 2 patients in the SOC group with surgery for tumor removal at the craniocervical junction did leak. In comparison of the two very early leakers (3 and 8 days post-operatively), it is reasonable to attribute these to DuraSeal as these early time-points would likely not allow adequate wound healing. It is noteworthy that both failures manifested as leaks through the skin and both employed only 1 application of DuraSeal intra-operatively. In terms of whether leaks manifested as through the skin vs. as a pseudomeningocele, as described previously, early leaks would be more likely due to failure of dural closure, while late leaks must also be attributed to poor tissue closure above the dural repair. Finally, the management of CSF leak is highly clinician-dependent, as to whether a patient is taken back to the operating room immediately or is managed conservatively with aspiration, lumbar drainage, or wound oversewing. Overall, while there were some notable differences between the leakers in each group, the low numbers (11 total leaks in 158 patients) make any subgroup analysis difficult and would likely not meet statistical significance.

FDA requested a Kaplan-Meier analysis for the time to event for the CSF leaks in both groups. The sponsor has provided tables comparing the overall leak rates between the two groups, as well as the distribution of early (<30 days) compared to late (>30 days) leakers. As described earlier, there were more early leakers (5) in the DuraSeal cohort compared to the control (1), however this is also partially due to adequate closure of the overlying tissues. The two leakers that are most attributable to early DuraSeal failure are those that leaked at 3 and 8 days, before

adequate tissue healing could occur. Once again, due to the low number of patients who leaked, no statistically valid conclusions can be drawn from this data. FDA requested an analysis of SOC early-leakers and their clinical outcomes as contrasted to DuraSeal intra-op successes. Of note, 7 patients (6.9%) in the DuraSeal group developed SSI in the first 30 days, but none developed meningitis, whereas the one patient in the control group that leaked in the first 30 days developed both an SSI and meningitis.

A question was raised by the FDA clinical reviewer as to whether the study was sufficiently powered to assess non-inferiority in post-operative CFS leak rates. The non-inferiority of post-operative leaks between the two treatment groups was never a claim to be evaluated by this clinical study. The incidence of post-operative leaks was a parameter to be reported and evaluated as part of the safety assessment. To test a non-inferiority hypothesis, the sponsor would have had to pre-specify a clinically meaningful margin of non-inferiority, beyond which DuraSeal would be considered clinically inferior to control, and sized the study to have 80% power to detect that difference as statistically significant. The difference in post-operative leak rates observed was between 2.4% and 2.8%, depending on whether one uses the binomial rates or the Kaplan Meier rates. To have powered the study to detect a difference that small as statistically significant would have required approximately 1600 DuraSeal and 800 control subjects. However, it is unlikely this small difference would have been the chosen margin of non-inferiority, which is the minimum difference that is considered clinically meaningful. On the other hand, if one asks, "Given the current sample size of 102 DuraSeal and 56 controls, how high would the post-operative leak rate have had to have been in the DuraSeal group in order for it to be significantly higher (and thus, not non-inferior) than the control group. The answer is the post-operative rate for DuraSeal would have had to have been approximately 15% (instead of ~8%). For the current analysis, the inference is that the observed difference in post-operative leak rates of approximately 2.5 % could have been due to chance ($p>0.57$).

FDA requested a stratified analysis of the MicroMyst applicator as compared to the Dual Liquid applicator with regard to CSF leakage. The choice of applicator was the surgeon's discretion. Overall, 55 patients were treated with the MicroMyst applicator, 42 patients with the Dual Liquid Applicator, and 5 patients with both techniques. Of note, a significantly higher proportion of patients operated on for Chiari malformation were treated with the Dual Liquid Applicator compared to the MicroMyst applicator (47.6% vs. 3.5%, $p< 0.001$). This led to a higher proportion of patients being treated with the Dual Liquid applicator in the cervical spine. In addition, this led to a larger number of patients undergoing duraplasty in this population. Given the fact that CSF leak occurred in 3/22 patients with Chiari malformation, it is unclear what role applicator type might have played. Overall, there was no difference in the intra-operative endpoint between the applicators and the incidence of device malfunctions (1/54 = 1.8% in the MicroMyst group vs. 2/40 = 4.8% in the Dual Liquid group). As described by the sponsor, there was a higher proportion of post-operative CSF leak using the Dual Liquid applicator (5/42 = 11.9%) compared to the Micromyst applicator (3/55 = 5.5%, not statistically significant), however this is confounded by the much higher rate of Chiari malformations treated with the Dual Liquid technique. While there were similar numbers of adverse events using each applicator, there were statistically significantly more when using the MicroMyst applicator in the "General Disorders and Administration Site Conditions" (mainly "pyrexia") and in the "Vascular Disorders" subgroups. A clinical explanation for these differences in terms of DuraSeal applicator is not apparent. Overall, FDA agrees with the sponsor that any observed differences between the two applicators in this study were likely due to the difference in surgical treatment populations and not due to the applicators themselves.

FDA requested that the sponsor explain the clinical benefit of their product given the fact that the primary effectiveness endpoint of intra-operative CSF leak did not correlate with the more clinically meaningful secondary endpoint of post-operative CSF leak (at 90 days). The sponsor responded by dividing their discussion into 5 parts:

- The importance of intra-operative sealing:
  - The sponsor detailed the risks associated with CSF leak and stated that intra-operative watertight dural closure is standard of care.
- The correlation between intraoperative sealing and a positive postoperative outcome:
  - The sponsor provided a post-hoc analysis where post-operative leakers (both treatment and control) were analyzed based on whether or not they were leak free intra-operatively. Using this approach,

15% of intra-operative leakers went on to develop post-operative leaks, compared to 5.8% of those who where leak free intra-operatively. This analysis was used to support a lack of intra-operative leak as a viable primary endpoint.

- A comparison of the low post-operative CSF leak rates found in the literature using adjunctive therapies to the low rate of post-operative CSF leaks in the study:
    - The sponsor conducted a detailed literature review of post-operative CSF leak rates in spinal surgery conducted for various indications (incidental, intradural exploration, tethered cord, Chiari malformation). They also provided a table summarizing this data.
- The clinical benefit of a reduced risk of disease transmission:
    - The sponsor stated that because DuraSeal is a synthetic material, and because its use allowed 100% intra-operative dural closure, this obviated the need for animal or human-derived products that carry a risk of disease transmission or immune reaction.
- The clinical benefit of ease of application of the DuraSeal Sealant:
    - The sponsor stated that there was a decrease in time-to-closure of 3 minutes (not statistically significant) and that 98/102 surgeons rated DuraSeal as "Easy" or Very Easy" to use.

DuraSeal was found to be superior to standard of care (SOC) in the primary effectiveness endpoint of intra-operative watertight closure. However, this finding did not correlate with post-operative CSF leak rates which were statistically similar at 90 days. FDA believes that post-operative CSF leak is a more clinically meaningful endpoint than intra-operative watertight closure, however, it is also noted that DuraSeal offers clinical benefits. First, the post-operative CSF leak rate for both DuraSeal and SOC were within the published leak rates for intentional dural opening of ~5-15%, depending on the spinal surgery indication. DuraSeal is very fast to set up and apply. While some problems have been noted in that the plungers in the Dual Liquid applicator sometimes come unattached from the applicator and it is common for the substance to clog in the applicator tip, requiring a new tip to be attached. However, given these drawbacks, DuraSeal is easier to use and takes less time than applying additional sutures, harvesting and sewing in muscle or fascial patches, or using fibrin glue which takes significant time to mix and heat (the surgeon must ask for it ~15-30 mins. ahead of time in order for it to be ready at the time of dural closure; this is particularly troublesome for incidental durotomies and can significantly delay dural repair/surgical time). DuraSeal also offers a better safety profile due to its synthetic nature compared to biological materials. Overall, although DuraSeal and SOC were similar in CSF leak rate at 90 days, the device offers a clinical benefit in the absence of significant safety concerns.

The panel will be asked to address the AE rates – is the higher rate of adverse events in the treated group clinically significant, and/or device-related?

With regard to the other important safety endpoints, there was no statistically or otherwise concerning difference in surgical site infection or wound healing. General neurological adverse events such as radiculopathy, paraplegia or other neurological deficit are also important, especially given the swelling characteristics of the device. The narratives of all AEs were reviewed in detail, and while, at first look there is an overall higher rate of SAE in the investigational group (29.4 vs 17.9%), this is not significant. Furthermore, on review of the AE narratives there was clearly too much clinical background noise to determine device effect (e.g. radiculopathy, paraplegia, and sensory loss patients had operations – spinal cord tumor and syrinx, with these expected outcomes).