

**EXECUTIVE SUMMARY**  
**INTRODUCTION**

Dear Panel Member,

This is the Executive Summary for the DuraSeal Dural Sealant System (P040034). The product has been reviewed by the Plastic and Reconstructive Surgery Branch of the Division of General, Restorative and Neurological Devices at the Center for Devices and Radiological Health of the Food and Drug Administration. Your time and effort in review of this application is greatly appreciated.

The Executive Summary contains FDA's summary review memo of the preclinical, clinical and statistical information. The memo contains the following sections:

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**MANUFACTURER INFORMATION**

Applicant name and address:

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 101A First Avenue

Waltham, MA 02451

Manufacturing sites/addresses

Manufacturing

Confluent Surgical, Inc.

101A First Avenue

Waltham, MA 02451

## **DEVICE DESCRIPTION**

A complete description with diagrams of the DuraSeal Dural Sealant System can be found in the device description section of the CDRM supplied by the sponsor. For completeness of the Executive Summary, a brief description of the device is presented here.

### Sealant

The sealant is composed of two solutions, a polyethylene glycol (PEG) ester solution and a trilycine amine solution referred to as the blue and clear precursor solutions. When mixed together, the precursors provide rapid in situ polymerization to form a hydrogel that seals the dura mater incisional site. The mixing of the precursors is accomplished in the DuraSeal delivery system as the materials exit the tip of the system.

### DuraSeal System Kit Components

<u>Component</u>	<u>Description</u>	<u>Quantity</u>
<u>Sealant Components</u>		
Powder vial	glass vial containing 20,000 Da N-hydroxy succinimide end capped PEG powder combined with FD&C #1 for visualization and BHT as a preservative. Vial is capped with halobutyl elastomer stopper	1 vial, 0.5g
Diluent syringe	polypropylene syringe containing sodium phosphate buffer	1 syringe, 2.5 mL
Clear precursor Syringe	polypropylene syringe containing Trilycine acetate in a 0.075M sodium borate decahydrate buffer	1 syringe, 2.5 mL
<u>Diluent Mixing Components</u>		
Biodome BIO-SET Injection cap	a polyethylene and acrylonitrile/butadiene/styrene component that is attached to the powder vial and Stopcock used to pierce the vial seal	1
Stopcock	plastic component that is attached to the BIOSET injection cap and the diluent syringe and is used to regulate the reconstitution of the powder vial contents with the phosphate buffer in the diluent syringe	1
<u>Delivery System Components</u>		
Plunger cap	plastic component that clips over both delivery syringe Plungers	1
Applicator*	plastic component that delivers the two polymer precursors to the spray tip	1

Spray tip\* plastic component used to mix and deliver the two polymer precursors to the surgical repair site 1

\*The applicator and spray tips are purchased from Hemaedics, Inc. The applicator and spray tip are class II devices and were cleared via K872565.

Product specifications

Powder vial with polyethylene glycol ester component

The powder vial contains the N-hydroxysuccinimide (NHS) capped polyethylene glycol (PEG) ester with FD&C Blue #1 dye and butylated hydroxytoluene (BHT). The dye is added to and blended with the PEG ester powder to provide a colorant for visualization during application of the sealant. The BHT is added as a preservative.

Specification

Characteristic

Measured by

Color

Molecular weight

% NHS substitution

Endotoxin

BHT

FD&C Blue Dye #1



GPC

NMR

LAL

HPLC

UV/Vis. Spec.

The sponsor notes that the PEG ester is sensitive to humidity, and to elevated temperatures. The PEG ester has a melting point of 45C, in-house testing has established that the material is stable in temperatures less than 35C. It is cold-shipped to the company in an inert atmosphere in sealed vials and is stored at -20C. The powder vial filling operation is performed at the company in a humidity-controlled, low oxygen/argon rich gas environment via use of a glove box.

Following vial filling, the vial is capped with an elastomer stopper and a Biodome BIO-SET Injection Cap is attached to the powder vial to provide a sharps-free access to the vial. The injection cap is a purchased “off the shelf” component and is composed of the following components:

- Cap – manufactured of Hostalen GD 7255 polyethylene
- Plastic vented needle – manufactured of Terlux 2802 TR, a methyl methacrylate/acrylonitrile/butadiene/styrene polymer
- Base – manufactured of Lacqtene 1020 FN 24 low density polyethylene

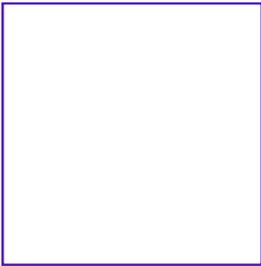
Diluent syringe

The syringe contains a sodium phosphate buffer (pH 4.0) that when mixed with the contents of the powder vial creates the blue precursor. A stopcock is attached to the syringe to regulate the flow of the diluent into the powder vial during reconstitution of the PEG ester powder with the buffer. The buffer, stopcock and 3 cc syringe are procured from approved suppliers. Final pH adjustment, syringe filling operation and stopcock attachment are performed at Confluent Surgical.

Clear precursor syringe with Trilysine Amine solution

The clear precursor syringe contains Trilysine acetate in sodium borate buffer solution (pH 10.2) with pre-attached Santoprene elastomeric cap. The acetate component is procured from a supplier in powder form.

Trilysine specifications

<u>Characteristic</u>	<u>Requirement</u>	<u>Measured by</u>
Appearance		Visible inspection
Identification		Mass spec
Purity		HPLC
Residual organic solvents		GC
Assay peptide content		Elemental analysis
Mass balance		Karl Fischer
Heavy metals		Atomic Absorp. Spec.
Endotoxin		LAL

Trilysine (amine) is manufactured by Bachem AG (Hauptstrasse 144 Bubendorf, Switzerland). Preparation of the borate buffer/trilysine solution and syringe filling are performed at Confluent Surgical.

DuraSeal Delivery System

The delivery system components consist of an applicator and spray tip that are already cleared by FDA. The applicator merges the 2 precursors to the spray tip for delivery to the surgical site. Intimate mixing of the precursors is accomplished in the swirl chamber, as they exit the tip of the sprayer. The spray tip is assembled from 2 components – the spray tip housing and an orifice cup. The components are press fitted together to form the spray tip and the assembly is performed at Confluent Surgical. A 3<sup>rd</sup> component of the delivery system, the plunger cap, aligns the 2 precursor syringe plungers to allow for simultaneous delivery of the 2 precursors in a 1:1 ratio.

Finished Kit – DuraSeal Dural Sealant System

The system is provided in a single, terminally-sterilized package that contains the components for preparation of the sealant and delivery system (i.e., applicator and spray tips). Final kit assembly is performed at Confluent Surgical. The components are placed into the package tray and sealed with a Tyvek lid. The package is sent (as a lot) to the irradiation sterilization facility and terminally sterilized (SAL =  $10^{-6}$ ) via E-beam irradiation at Nutek Corporation. The minimum sterilization dose is 25 kGy.

Under “Description of the DuraSeal Sealant Application”, the sponsor describes the application process. They also note that the product can be used for one hour after reconstitution. Specifications for the finished product are given in the Table below:

Essential Device Properties for the DuraSeal Dural Sealant System (not all tests, requirements are listed)

Design characteristic

Specification

Polymer specifications:

Reconstitution time

Gel time

Pot life

Swelling

In vitro absorp.

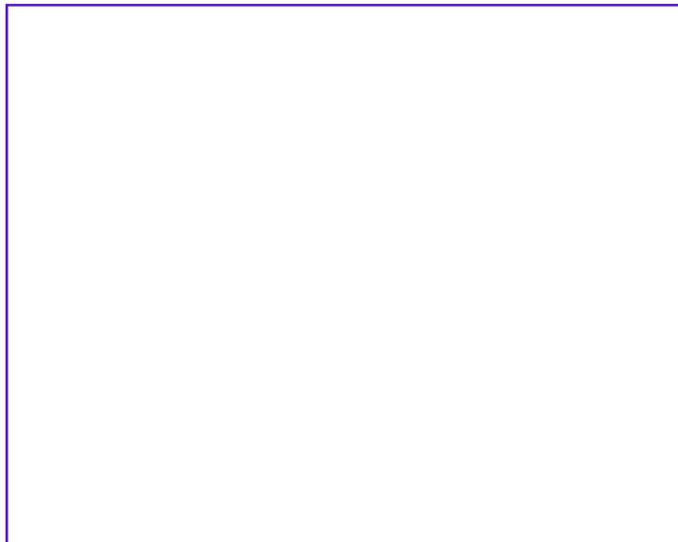
Syringe/application specifications:

Application

Application-press. integrity

Uniform gel application

Sealant pyrogenicity



**INDICATIONS FOR USE**

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

## PRECLINICAL

The preclinical review focuses on the chemistry/toxicology information. Recall from the device description section that the polymerized sealant results from the mixing of the 2 reactants: PEG end-capped with reactive N-hydroxysuccinimide groups, and trilysine. Trilysine is the nucleophilic substituent that cross-links PEG.

### 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

The sponsor cites clinical experience in Europe as supportive safety information with respect to toxicology of the device components and for patient exposure calculations. In their European experience they found that up to 5 grams of sealant are used for a typical surgical procedure. This quantity of the device provides a 2 mm thick film covering a surface area of 25 cm<sup>2</sup>. In a 70 Kg patient the amount of the device administered would be 71.4 mg/Kg.

### Individual component toxicology review

PEG (end modified PEG ester, CAS No. 25322-68-3): PEG is widely used in the pharmaceutical industry in both solid and liquid forms. The sponsor notes that there are 2 PEG-based hydrogels that are legally marketed surgical sealants: FocalSeal by Genzyme and CoSeal by Cohesion Technologies.

The FocalSeal polymer consists of PEG with an average molecular weight of 31,500 daltons whereas the subject device consists of PEG with an average molecular weight of 20,000 daltons.

### Clearance/PEG

Papers were provided to substantiate the sponsor's assertion that:

- a. plasma concentration time curves of higher MW PEGs were substantially greater than those of PEG of lower MWs
- b. the  $t^{1/2}$  of PEG polymers progressively increases as MW increases
- c. urinary clearance appears to be inversely related to PEG MW

To address PEG clearance in the clinical study the sponsor has performed the following evaluations performed pre-operatively, at discharge or 7 days and at 3 months:

- a. hematology plus platelets, excluding differentials
- b. electrolytes (Na, K, Cl, bicarbonate)
- c. renal function (BUN and creatinine)
- d. glucose levels

No clinically significant alterations in these parameters were noted.

Trilysine: trilysine is a low molecular weight molecule that has 4 primary amine functional groups that take part in the nucleophile substitution reaction, displacing N-hydroxy succinimide (NHS). The amine is the synthesis product of L-lysine amino acids. L-lysine, itself, is a naturally occurring amino acid. The quantity of trilysine in one application of the sealant is 0.151 mg/kg. An extensive search of the toxicology literature databases found no toxicology information concerning trilysine. This search included the following databases:

- Registry of Toxic Effects of Chemical Substances (RTECS)
- Hazardous Substance Data Bank
- Integrated Risk Information System
- Chemical Carcinogenesis Research Information System
- Genetic Toxicology
- TOXLINE
- Environmental Mutagen Information Center
- Developmental and Reproductive Toxicology
- Toxics Release Inventory
- National Library of Medicine
- Internet Grateful Med

Additional information regarding the synthesis of trilysine retrieved from previous review: This material has been evaluated in the preclinical animal evaluations and found not to cause toxicity.

NHS will be generated as a breakdown product during degradation of the sealant. The sponsor conducted a clearance assessment to determine if PEG metabolism would influence kidney or blood parameters and found no clinically significant result. NHS

breakdown was generically assessed for its influence on kidney and blood parameters in this clearance evaluation. The sponsor estimates that patients will be exposed to 0.33 mg/kg NHS. I could not find any information in toxicology database searches, nor could the sponsor.

Sodium borate: LD<sub>50</sub>'s for human oral (709 mg/Kg), mouse intraperitoneal (2711 mg/Kg), mouse intravenous (1320 mg/Kg) and rabbit subcutaneous (150 mg/Kg) are 100 fold to greater than 1000 fold higher than what patients in this clinical use will experience. Borate is the conjugate base of boric acid which is used widely as an antiseptic. The quantity of borate in one application is 0.914 mg/kg. There is no evidence of either a carcinogenic or mutagenic effect of this compound. Boron compounds do not appear to be metabolized in humans or animals as evidenced by the excretion of 90% of an administered dose of boron. Boron is primarily excreted in the urine, regardless of the route of administration.

Sodium phosphate: LD<sub>50</sub>'s for rat oral (8290 mg/Kg) and rat intraperitoneal (250 mg/Kg) are 1000 fold and greater higher than what patients in this clinical use will experience. The quantity of sodium phosphate in one application of the sealant is 0.0381 mg/kg. Sodium phosphate is a buffer that is widely used in clinical settings.

FD&C Blue #1: The quantity of the dye in one application of the device will be approximately 0.0071 mg/Kg (7.1 µg). Tumorigenicity evaluations of the dye are summarized below:

Organism	route	manifestation	dose
Rat	subcu	tumorigenic	5500 mg/Kg – weekly injections
Rat	parenteral	tumorigenic	4580 mg/Kg – weekly injections
Rat	subcu	tumorigenic	2000 mg/Kg – weekly injections
Mouse	subcu	behavioral	4600 mg/Kg

The amount of the dye in the product is approximately 0.001% of the doses indicated in these studies. References provided by the sponsor regarding the ability of brilliant blue dye to induce cellular transformation indicated that the transformation event, i.e., fibrosarcomatous lesions found at the injection site, were likely due to the repeated, mechanical disruption of the tissue and high dose rather than due to a strong carcinogenic effect.

FD&C Blue #1 dye is listed as a certified color in 21 CFR 82. It is mainly used in foods intended for use in dairy products, beverages, dessert powders, candies, etc. The amount contained in the device, the extensive genotoxicity evaluations conducted by the sponsor (see biocompatibility evaluations below) and the information cited from research literature that indicate effects only at extremely high, multiple repeat doses, provide reasonable assurance of the safety of this chemical component.

Additional information submitted: Toxicity has been reported in association with FD&C Blue #1 tinting of enteral feedings, intended as a means of visually detecting pulmonary

aspiration. Patients in one report received approximately 1 mg/kg/d of FD&C Blue #1 dye, well below the limit set by FDA (FD&C Blue #1 is a water soluble dye allowed by FDA for use in foods, drugs and cosmetics, based on numerous studies in animals. Data from life-exposure animal studies supports an ADI [acceptable daily intake] of FD&C Blue #1 of 12.0 mg/kg/day. For 70 kg patients, this translates to a daily limit of 42 mL of a 2% FD&C Blue #1 solution or 840 mg/day.), but significantly greater than the quantity of dye in the sealant. The amount of dye used in the symptomatic enteral feeding patients was several orders of magnitude greater than that used in DuraSeal applications. In addition, use of DuraSeal is a one-time application of 7.1 micrograms of the dye and therefore far below the quantities that have been noted to elicit toxicity. The canine and rodent preclinical animal evaluations used significant quantities of the dye and toxicities were not noted.

Butylated hydroxytoluene: Butylated hydroxytoluene is an antioxidant and has been designated as GRAS for use in foods since 1959. It had received FDA approval as a food additive and preservative by FDA in 1954. BHT is incorporated into the device to increase shelf life of the polymer. The amount per application is < 0.1 mg. The WHO recommendation for ADI of BHT is 0.125 mg/kg. The amount of BHT per application is 0.0013 mg/kg. There have been studies regarding short and long term toxicity, carcinogenicity, reproductive toxicity, teratogenicity, genotoxicity, hepatotoxicity, nephrotoxicity, and pulmonary toxicity of BHT. The no effect level observed in mice and rats was 5000 ppm in the diet (equivalent to 250 mg/kg) and 1000 ppm (equivalent to 50 mg/kg), respectively.

#### Toluene, pyridine and methylene chloride

These chemicals are used in the synthesis of the PEG ester. These chemicals are included in the product specification for total volatile organic impurities (400 ppm by GC) for the PEG ester. If each were allowed the maximum 400 ppm, for a 70 kg patient treated with 0.5 g of PEG ester, the exposure (per chemical) would be 0.0029 mg/kg. This concentration is far below the toxic dose per chemical as found in the RTECS database.

For toluene, using the IRIS database, no human data and inadequate animal data has been found to determine if the chemical is a potential carcinogen. The majority of genotoxicity assays were negative. The NOAEL in rats was determined to be 302 mg/kg/day. Pyridine's NOAEL was determined in rats to be 1 mg/kg/day. Pyridine has not undergone a complete carcinogenicity evaluation to date. Inadequate information to determine if methylene chloride is a human carcinogen is available. The NOAEL for methylene chloride is 5 mg/kg/day. All of these chemicals, as found in the product, are 300 fold lower than the lowest (pyridine, 1 mg/kg/day) NOAEL. Still, although the preclinical testing does not indicate that the product is toxic, nor does the toxicity data suggest that the product with chemicals at these levels poses safety concerns, a deficiency requesting that the organic volatiles be reduced further was presented to the sponsor. The current product release specifications were requested to be diminished, thereby decreasing potential patient exposure. The deficiencies and sponsor reply will be provided in the second mail-out. The sponsor did comply with FDA's request.

Additional information retrieved from the sponsor's IDE:

Toluene, pyridine and methylene chloride are included in the specification for total volatile organic impurities (400 by GC – see QC/QA specifications above) for the PEG ester. If a 70 Kg patient is treated with an estimated 0.5 g of the PEG ester and assuming that each chemical was allowed the maximum limit, i.e., 400 ppm, the calculated exposure would be 0.0029 mg/Kg. The sponsor provided the published toxicity data for toluene, pyridine and methylene chloride.

Toluene – from 52 gm/m<sup>3</sup> and 357 mg/Kg – 14400 ppm/7h

Pyridine – from 360 mg/Kg to 28.5 g/m<sup>3</sup>/hr

Methylene chloride – from 357 mg/Kg to 5350 mg/Kg

Toluene is not listed as a carcinogen. EPA has set a limit for exposure to Toluene of 1 mg/L of drinking water. Pyridine has not been classified as a carcinogen – no studies in humans or animals have been done. Pyridine is used as a flavoring agent in the preparation of foods. The EPA recommends that exposure of children to methylene chloride be limited to less than 10 mg/L for 1 day or 2 mg/L for 10 days. Methylene chloride is commonly used in the process of decaffeinating coffee beans.

Glutaric anhydride

As the sponsor notes, the glutaric anhydride and NHS levels are not stated as a release specification. The amount of glutaric anhydride needed to fully functionalize 1 gram of 4 arm, 20,000 MW PEG would be 0.33 mg/Kg. Two citations were provided for glutaric anhydride – 540 mg/Kg and 1780 mg/Kg were LD<sub>50</sub>'s for oral and skin exposures in the rat and rabbit, respectively. No toxicology information was found for NHS but the sponsor notes that the device has been evaluated in a series of *in vitro*, *in vivo*, acute and chronic preclinical tests – many of which were performed at multiples of the expected human dose.

Conclusion

The various chemicals identified in the product have toxicities **only** associated with large, repeated doses. The anticipated dose of each chemical anticipated in humans is far below the published toxicity values. Large excess of these chemicals was evaluated in various animal preclinical studies and in 4 mutagenicity/genotoxicity evaluations (see following information). No toxic findings were noted. In addition, the device has been used in a clinical trial in Europe and no adverse device related findings were noted. No additional information is requested regarding the toxicology of the device components.

Preclinical studies

The sponsor has conducted some key functional tests to more completely define the sealant. These tests are used as product release parameters and they provide a physicochemical description of the product:

- Gel time/pot life
- In vitro disappearance (real time and accelerated conditions)
- Swelling

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 pot life assessment evaluated the gel time of the hydrogel after 1 hour following reconstitution of the blue precursor. The label specifies that the sealant should be used within 60 minutes of preparation of the blue precursor.

Specification: =

In vitro disappearance: The purpose of this test is to evaluate in vitro disappearance of the formed hydrogel, which is defined as the time it takes for the formed hydrogel to visibly dissolve when immersed in a PBS solution, pH 7.4, at 60.4C. These are the conditions of the accelerated test.

Specification:

Swelling: The purpose of this test is to evaluate the extent of swelling of the formed hydrogel, which is defined as the percent weight gain resulting from 24 hour immersion in 37C PBS. This assessment is an indirect measure of cross-link density.

Specification:

#### Delivery system

The device delivery system is comprised of the applicator, spray tips and the plunger cap. The applicator and spray tips are purchased as separate, non-sterile components from Hemaedics, Inc., and assembled at Confluent Surgical. The plunger cap is purchased as a separate non-sterile component from Scitech Plastics Group. Mechanical testing has been performed on the delivery system to ensure that it meets the design requirements and to ensure compatibility with the device.

#### Applicator Mechanical Integrity Testing

Mechanical integrity testing of the applicator has been conducted to ensure that the applicator can withstand pressures to which the system will be exposed during clinical use. The applicator provides a delivery mechanism for the clear and blue precursors to the application site. A minimum pressure specification that the applicator is to withstand was initially set to 100 psi. An evaluation regarding the actual pressure experienced when spraying polymerized gel through the applicator/tip determined that a pressure of approximately 31.8 psi occurred in the applicator. The specification was revised from 100 psi to 68 psi. The instructions for use indicate that once a spray tip is clogged, use should

be discontinued. Normal application pressure through an unclogged spray tip is 17.9 psi.

In the evaluation 19 applicators containing spray tips with acetal orifice cups and 60 spray tips with nylon orifice cups were evaluated. The spray tips met the 100 psi original specification (acetal cups) and the revised 68 psi specification (nylon spray cups).

#### Applicator Sprayability Testing

The purpose of the test is to verify that the gel will be dispersed in a uniform pattern less than 10 mm in diameter when the applicator is 2-4 cm from the target tissue. 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.

In the evaluation, acetal cups and nylon cups were tested with the applicators. The sprayed gel conformed to the specification.

#### Environmental/Stability evaluations

Testing evaluated the freeze-thaw stability of the hydrogel sealant by examining the functional performance of the precursor components following exposure to repeated freeze/thaw cycles between -20 and 35C over the course of 32 days. Under normal conditions, product is stored at -20C until it reaches the end-user. Recommended storage indicates that product is to be stored at or below 25C. In the evaluation, the sponsor conducted the following tests:

- Gel time/pot life
- In vitro disappearance (real time and accelerated conditions)
- Swelling
- Reconstitution time
- Buffer pH
- PEG ester vial oxygen content
- Modulus

The kits were stored various periods of time at -20 or 35C and then tested. Length of time at -20C ranged from 0-28 days, and length of time at 35C ranged from 4-32 days. The specifications are as listed above per test. For modulus, there was no reference value and evaluation was done solely for informational purposes.

Results: The device met all specifications and were equivalent to control. Modulus was measured at  $32.6 \pm 8.8$  kPa.

#### Freeze-thaw stability of the applicator (y-connector) and spray tip

The purpose of the evaluation was to demonstrate that the applicator/spray tip delivery system would not be affected by the freeze-thaw cycling. Components were submitted to determine the torque to attach the spray tip, and the torque to deform the spray tip. Following processing, the components were evaluated for the following attributes:

- Visual inspection for cracks and component integrity
- Fluid injection for leak testing
- Torque to attach spray tip does not affect component integrity or sprayability
- Torque to attach and torque to failure of syringe luer and tip luer connections

Acceptance criteria:

- Applicator and spray tip are free from cracks, physical damage or gross cosmetic imperfections
- Applicator with spray tip is free from leaks when fluid is injected and spray tip exit is blocked
- Sprayability of final assembly is acceptable, i.e., liquids are atomized
- Torque required to attach spray tip during normal use is less than that required to torque to failure

Results: The components passed the acceptance criteria.

#### E-beam sterilization of DuraSeal Polymer kit at maximum radiation dose (interim report)

Dose mapping studies for the device have shown dosimeter values varying from 28 to 41 kGy. The study was undertaken to evaluate the effect of high irradiation doses on the functionality and stability of the sealant precursors. Product was sterilized using a 41 kGy dose. Following processing, kits were stored at 25C for intervals up to 2 years. This is an interim report in that data is available up to the 6 month time point. For evaluation of the effect of the high dose radiation, the sponsor is comparing stability data obtained from the shelf life study which has real time information out to 9 months. The time intervals for evaluation are: 13 weeks, 26 weeks, 39 weeks, 52 weeks, 78 weeks, and 104 weeks. The sponsor assessed the following parameters:

- Gel time/pot life
- In vitro disappearance (real time and accelerated conditions)
- Swelling
- Reconstitution time
- Buffer pH
- PEG ester vial oxygen content
- Viscosity

## Results:

- Gel time/pot life passed
- In vitro disappearance: using the accelerated 4 day procedure, the sponsor missed the 4 day assessment and noted all material had disappeared by 5 days
- Swelling: the high dose material swelled slightly more -130% at 15 weeks compared to approximately 100% for control, but was well within the <200% specification
- Buffer pH passed
- Oxygen – steady increase for control and for high dose irradiation from approximately 0.15% to <0.6% at 26 weeks, but still within the <1% specification
- Viscosity – remained constant over time

## Packaging

The device is provided in a terminally sterilized package that contains the precursor and delivery system components placed into a polyethylene terephthalate-glycol (PETG) tray and sealed with a Tyvek 1073B lid. For delivery to the customer, 5 trays 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 25 each – 5 shelf boxes containing 5 trays each. Twenty-one refrigerant bricks are placed around the product in an insulated shipping box. Studies were conducted to verify that the packaging materials and configuration are acceptable for use. The testing included:

- Accelerated aging of the packaging tray and Tyvek lid
- Ship testing in accordance with International Safe Transit Association (ISTA 1A) Vibration and Drop testing of the final shipment packaging
- Microbial Challenge of the Tyvek lid
- Tray porosity testing

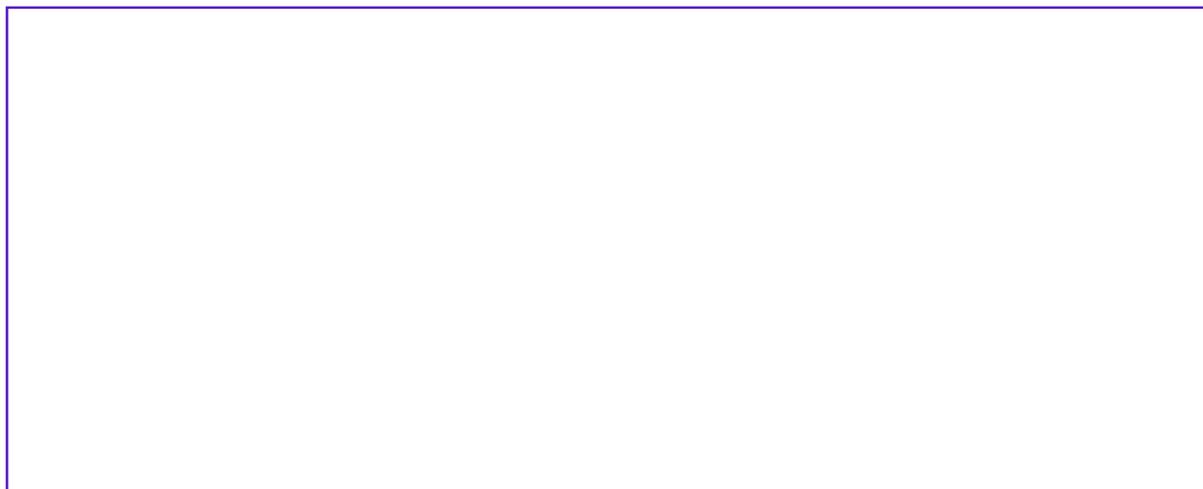
Results: The device/packaging configuration passed the criteria regarding the Tyvek lid test and the ISTA 1A test. In the microbial challenge assessment, the packaging material retained or excluded 99.99924 or greater % of the microbial challenge. The sponsor indicates that the data demonstrate that the Tyvek lid is an effective microbial barrier. The tray passed the porosity evaluation.

## Shelf-life testing/ongoing evaluations

The sponsor is conducting an expiration date evaluation using real-time as well as accelerated testing conditions. Product will be evaluated for the following:

- Visual assessment – all system components are intact with no visual evidence of deterioration
- Hydrogel performance – gel time/pot life, in vitro disappearance time and swelling
- Determination of buffer pH and oxygen content in PEG ester powder vial
- Applicator performance – using all kit components to evaluate dispersion pattern

- of prepared hydrogel and leak integrity of applicator
- Packaging assessment – verify package integrity, seal strength, visual assessments for no voids or crimping and labeling legibility



### Biocompatibility

Biocompatibility testing of the device was conducted on test samples representative of the final device with the following noted exceptions:

- A vial spike rather than the Biodome BIO-SET Injection Cap was used to transfer the diluent into the PEG ester powder vial. The Biodome BIO-SET cap has passed biocompatibility evaluations conducted by its manufacturer.
- Initial applicator testing biocompatibility was performed with the acetal orifice cup. Additional testing is ongoing to evaluate the nylon material currently being used for the spray tip orifice cup. The testing was completed and all passing results were noted.

Using the ISO-10993 Biological Evaluation of Medical Devices standard for biocompatibility test selection, the sponsor identified the hydrogel as a tissue/bone contacting implant of permanent contact duration, and the delivery system components (applicator and spray tip) as an externally communicating device with tissue/bone contact of limited contact duration.

### Test extract preparation

Extracts were prepared in the following manner: the clear and blue precursors were reconstituted in accordance with the instructions for use. The precursors were sprayed into sterilized vessels, and 0.9% saline was poured over the hydrogel at a ratio of 4 g of test article per 16 mL of saline (resulting in a 20% test article solution with an implant concentration in the solution of 200.7 mg/mL: hydrogel density = 1.018;  $4 \text{ g}/16 \text{ mL} = ((4/1.018)+16)$  or 19.929 mL;  $4 \text{ g}/19.929 \text{ mL} = 200.7 \text{ mg/mL}$ ). The container was incubated at 37C for 24 hours until the gel completely dissolved. Borate buffer

dissolution into the saline solution raised the pH to 9 and therefore for certain pH-sensitive tests, the pH had to be adjusted to 7.4. Following pH adjustment, the solution was diluted at a 1:1 ratio using saline. This method of sample preparation, the sponsor asserts, ensures that all extractables, unreacted polymer, and all degradation byproducts are present in the final solution to be tested.

ISO-10993 suggests the following tests be conducted for medical devices having permanent tissue/bone contact exposure:

- Cytotoxicity
- Sensitization
- Irritation
- Systemic toxicity
- Subacute or subchronic toxicity
- Genotoxicity
- Implantation
- Chronic toxicity
- Carcinogenicity

For medical externally communicating devices having tissue/bone contact of limited contact duration, the following tests are recommended:

- Cytotoxicity
- Sensitization
- Irritation

The sponsor conducted the following tests and determined the correlated results:

Sealant

Cytotoxicity	Pass
Sensitization	Pass
Intracutaneous reactivity	Pass
Acute systemic toxicity	Pass
Pyrogenicity	Pass
Subchronic toxicity	Pass, slight irritant

Genotoxicity

- |                           |      |
|---------------------------|------|
| 1. Ames mutagenicity      | Pass |
| 2. Chromosomal aberration | Pass |

The percentage of cells with structural aberrations in the test article (25 µL sample; range was 25, 50 and 100 µL) dissolution-treated groups was significantly increased above that of the dissolution blank control at 4 hours of incubation in the absence of metabolic activation. However there was no dose response and the percentage of cells with aberrations was within the historical solvent control range and therefore the effect was determined to be biologically insignificant. The percentage of cells with structural aberrations in the test article dissolution-treated groups was significantly increased above that of the dissolution blank control at 4 hours of incubation in the presence of metabolic

activation and the effect was dose dependent. Again, however, the percentage of cells with aberrations was within the historical solvent control range and therefore the effect was determined to be biologically insignificant. The percentage of cells with structural or numerical aberrations in the test article-dissolution treated group in the absence of metabolic activation at 20 hours was not significantly increased above control.

3. Mouse micronucleus	Pass
4. Mouse lymphoma	Pass
Implantation (2 weeks)	Pass, slight irritant
Subcutaneous Implantation (10 days)	Pass
Hemolysis	Pass

Chronic toxicity and carcinogenicity evaluations were not conducted. The sponsor states that testing was not conducted for the following reasons:

- No evidence of mutagenic activity in 4 genotoxicity evaluations
- Exposure to the product is of a limited duration – 4 to 8 weeks
- PEG metabolism and clearance is understood
- Trilysine amine is a by-product of lysine
- PEG, FD&C Blue Dye #1 and BHT have a well established history of use in the production of foods and pharmaceuticals and the levels to which patients will be exposed are well below the levels used in food and other medical device applications

FDA concurs with this assessment and agrees that carcinogenicity testing is not warranted.

#### Applicator

Cytotoxicity	Pass
USP Physicochemical Studies, i.e., aqueous and non-aqueous extracts	Pass

Test includes assessments of extracts for non-volatile residues, residues on ignition, heavy metal determination, and buffering capacity

#### Applicator with Nylon Orifice Cup

Systemic toxicity	Pass
Cytotoxicity	Pass

#### BIO-SET Plastic Needle

Systemic toxicity (mouse)	Pass
Irritation	Pass
USP Physicochemical Study	Pass

**Stelmi Stopper (vial stopper)**

USP 23 NF 18 <381>, Elastomeric Closures for Injections Pass

The testing includes evaluations of the following parameters: ash%, specific gravity, turbidity, reducing agents, heavy metals (lead and zinc), pH change, total extractables, durometer, 100% modulus, elongation (%), tensile strength, compression set (%), and cytotoxicity

**Flexible Syringe Cap (provided by B. Braun)**

B. Braun provided a letter attesting that the cap had passed biocompatibility evaluations.

**Conclusion**

The device has met the recommended, standard biocompatibility evaluations. No additional biocompatibility or toxicology testing is required.

**Animal and in vitro preclinical (biological) evaluations****In vitro proliferative effects of DuraSeal in various human cancer cell lines**

The study was designed to determine if the DuraSeal device could stimulate or inhibit proliferation of 4 human cancer cell lines. For the evaluation, DuraSeal was prepared per instructions for use and sprayed onto sterile plastic tissue culture plates to a thickness of 1 mm. The gel was scraped off the plates and pieces were weighed and then incubated with PBS. The following human cancer cell lines were evaluated for their response to incubation with the gel pieces:

- U-87 MG: human glioblastoma
- NIH:OVCAR-3: human ovarian carcinoma
- A549: human lung adenocarcinoma
- HT-29: human colon carcinoma

The gel pieces were placed in tissue culture well inserts suspended above cells previously plated in 24 well plates. After 3 days of incubation, the cells were measured with the MTT assay. The MTT assay measures proliferative responses based upon mitochondrial oxidative reduction of the MTT substrate.

Results: DuraSeal did not have a stimulatory or inhibitory effect on the 4 cell lines.

**Canine Cranial Sealing Study**

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.

Results: All dogs remained neurologically intact. At re-exploration, 11/11 control dogs showed CSF leakage at < 20 cm H<sub>2</sub>O – 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<sub>2</sub>O; normal CSF pressure in dogs is

reported to be approximately 9 cm H<sub>2</sub>O). 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<sub>2</sub>O in controls and 53, 37, 42 and 48 cm H<sub>2</sub>O 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.

#### DuraSeal MR and CT Imaging: Evaluation in a Canine Craniotomy Model

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.

Results: 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-adjointing enhancement, until the 10 week time point, when there is near total resorption with virtually no residual enhancement.”
- 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.

#### Rat Brain Parenchymal Implant Study

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.

Results: 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 the rat following injection into the brain

The device was evaluated for potential neurotoxicity following injection into the brain of the rat. Of 26 animals prepared with instrumentation, 14 had a single lateral ventricle cannulation and 12 had cisterna magna cannulation. For each cannulation type, half of the animals were injected via the cannula with the test article or control solution (22  $\mu$ L for lateral ventricle and 19  $\mu$ L for cisterna magna). Detailed health examinations and neurologic assessments were conducted at pretreatment and days 1, 2, 4 and 14.

Results: Under the conditions of the study, there was no significant evidence of neurotoxicity from the test extract injected into the brain of the rats. Daily clinical observations, neurologic assessments, body weights, necropsy findings, organ weights, and organ/body weight ratios were judged to be within acceptable limits and were similar between and within test and control treatment groups. No encapsulation was macroscopically observed at any test or control cannulation site and microscopic evaluation revealed no evidence of a treatment related response.

#### Evaluation of DuraSeal Persistence Following Subcutaneous Implantation in the Rat

In this evaluation, various formulations of DuraSeal were implanted into subcutaneous sites in rats. Plugs of material polymerized for 10 minutes, 0.25 x 0.25 inches in diameter and length were implanted and then excised at 2, 4, 6, 8, 10, 12 and 14 weeks. The animals were observed daily and, at take-down, the implantation sites were examined macroscopically for persistence and extent of degradation.

Results: All animals appeared clinically normal throughout the duration of the study. The various formulations were determined to be degraded within 8 weeks or of shorter duration:

DuraSeal (Avail)	6 weeks
DuraSeal (CSI)	8 weeks
DuraSeal II (CSI)	4 weeks

Additional information was requested regarding these findings. The deficiency and the sponsor's reply will be provided in the second mail-out.

#### Study for Effects on Embryo-Fetal Development with DuraSeal in Rats Following Intraperitoneal Administration

The study was conducted to determine the developmental toxicity, including the teratogenic potential of the product in rats following a single intraperitoneal or subcutaneous administration. The study was composed of 2 treatment groups (DuraSeal and SprayGel) and a control group. Each group contained 25 time-mated female rats. DuraSeal was administered via subcutaneous injection once on Day 6 of gestation at 0.1 mL/animal (0.3909 mL/kg). The control article (0.9% sodium chloride, 0.2 mL/animal, 0.7858 mL/kg) was administered via intraperitoneal injection once on Day 6 of gestation. Observations of animals during gestation included clinical signs, body weights, and food consumption. Each dam was subjected to a necropsy, including a uterine examination in which the total number of implantations, early and late resorptions, live and dead fetuses, sex, and individual fetal body weights were recorded. The total number of corpora lutea on each ovary was also recorded. Gravid uterine weights were recorded, and adjusted body weight changes were calculated. All fetuses were given an external examination and processed for visceral or skeletal examination. Malformations and developmental variations were recorded.

Results: One animal died shortly after dosing on Day 6 of gestation but the death was determined to be caused by the accidental severing of an artery during dosing and was determined not to be device-related. No test article related clinical findings were noted. Some tissue discoloration was observed but was believed to be due to the dosing procedure, i.e., subcutaneous injection. No test article related changes in body weight nor in food consumption were documented. No abnormal findings were observed in the maternal necropsy nor in the uterine and ovarian examinations. The pregnancy rate was 92% and there were no spontaneous abortions or early deliveries. There were no changes in the numbers of corpora lutea, implantations, viable and nonviable fetuses, or resorptions in the treatment groups when compared with the control group. Therefore, there were no changes in the preimplantation or postimplantation indices. Fetal sex ratio and litter size were comparable to control and the gravid uterine weight, body weight and weight gains were also comparable to control groups. There were no test article related external abnormalities observed. One fetus treated with SprayGel was noted to have omphalocele and microphthalmia but these malformations were within the historical reference incidence of the laboratory. No visceral malformations or test article-related

skeletal malformations were observed. The incidence of rudimentary ribs observed in the DuraSeal group were well within the historical incidence for the laboratory.

In conclusion, the test articles, SprayGel and DuraSeal did not have developmental toxicities or teratogenic effects on any parameters measured in the dams or fetuses.

#### Pre-clinical Studies Conclusions

The sponsor and FDA have reviewed the device chemical components for potential toxicities. The scientific literature indicates for most of the components that no toxicities have been noted, or where toxicities have been observed, they were observed with large amounts of the chemicals and when given in repeat dose manner. Patients will be exposed to the chemicals at concentrations several orders lower than those cited in toxicology database information, and at one time. The sponsor has conducted the recommended biocompatibility evaluations for a device having permanent contact with tissue/bone. The findings demonstrate that the product can be safely anticipated to be biocompatible in humans. Animal preclinical test evaluations, including the use of the device as intended clinically, clearly showed that the product is well-tolerated and safe.

## **CLINICAL**

DuraSeal has been the subject of two clinical studies: a pilot study and a pivotal study.

*Pilot study:* The pilot study was conducted between 2/2002 and 9/2003 in the Netherlands. This study was a prospective, single arm, single center, non-randomized investigation to examine the safety and performance of DuraSeal in patient undergoing elective cranial or spinal surgery. The primary efficacy endpoint was the presence or absence of CSF leak after DuraSeal application during Valsalva mane uver up to 20 cm H<sub>2</sub>O. Success was defined as no CSF leak after DuraSeal application. Safety data including all adverse events were collected. This data was used to support the initiation of the pivotal US study.

*Pivotal study:* Under the IDE the sponsor conducted the pivotal study in support of this PMA application.

### **Clinical Study Design:**

The choice of the clinical study design was reviewed by both the sponsor and FDA. The study design was influenced by the following factors:

- There are no FDA-approved dural sealant products. Fibrin glue is used off-label for sealing dural CSF leaks, however it has never been approved for this indication. Standard of care treatment was considered for use as a control but it was felt that a heterogenous control population would create difficulties in the analysis of the safety and effectiveness information.
- A clinical endpoint regarding CSF leakage was considered instead of the intraoperative surrogate endpoint. It was felt that an intraoperative leak assessment, in addition to a 3 month safety evaluation for CSF leak and infection, would reasonably provide a safety and effectiveness profile for this product's use as an adjunct to sutured dural closure.

FDA received input from a Neurological Devices Advisory Panel member regarding the study design prior to approving the IDE.

- Objective: To evaluate the safety and effectiveness of the DuraSeal  sealant system as an adjunct to sutured repair during cranial surgery to provide a watertight closure.
- Design: Prospective, multi-center, non-randomized, single-arm clinical study.
- Patient selection: Patients undergoing elective cranial surgery were screened for inclusion in the study. Baseline screening included a physical exam, mRS, baseline CT imaging, baseline lab tests and collection of information about baseline medications. If patients met the pre-operative inclusion and exclusion criteria, they were consented for participation in the study. To receive treatment, patient must then also meet the intraoperative inclusion and exclusion criteria (see below).

- Pre-operative criteria:
  - Inclusion criteria:
    - Age between 18 and 75.
    - Scheduled for an elective cranial procedure with a dural incision
    - Surgical wound classification is expected to be Class I/clean
    - Informed consent
  - Exclusion:
    - Translabyrinthine, transsphenoidal, transoral, and/or any other procedure that penetrates air sinus or mastoid air cells (not excluding superficial penetration).
    - Prior procedure in same location
    - Patient had prior chemotherapy within 6 months, or planned chemo prior to last follow-up.
    - Prior radiation to the site or planned radiation within 1 month
    - Known hydrocephalus (ICP > 22 cm H<sub>2</sub>O)
    - Malignant disease with a life expectancy less than 6 months.
    - Pre-existing EVD or lumbar drain
    - Patient cannot tolerate Valsalva maneuvers or had a shunt that will prevent transient elevation of ICP with Valsalva.
    - Systemic or location infection
    - Known allergy to device components
    - Pregnant or breast feeding females
    - h/o head trauma
    - Chronic steroid treatment not discontinued at least 6 weeks prior to trial
    - Autoimmune disease or compromised immune system
    - Uncontrolled diabetes
    - Creatinine > 2.0
    - Total bilirubin > 2.5
    - PTT > 35, INR > 1.2, receiving ASA or NSAIDS
    - Participating in another clinical trial.
    - Unlikely to comply with follow-up
    - Receiving warfarin or heparin
  
- Intraoperative criteria
  - Inclusion
    - Surgical wound is Class I/Clean
    - Durotomy is > 2 cm in length
    - Dural margin is at least 3mm from bony edge
    - CSF leak must be present after primary dural closure either spontaneous or after Valsalva to 20 cm H<sub>2</sub>O
  - Exclusion
    - Incidental finding of any pre-operative exclusion criteria
    - Use of synthetic or non-autologous duraplasty material in primary closure

- Gap of greater than 2mm remaining after primary closure
- Primary efficacy endpoint
  - Success defined as no CSF leakage from dural repair after Valsalva to 20 cm H<sub>2</sub>O for 5-10 seconds.
  - Failure defined as any CSF leakage after up to two DuraSeal applications and with Valsalva.
- Safety Endpoints
  - CSF leak or pseudomeningocele related surgical intervention within 3 months post-op or
  - CSF leak confirmed by diagnostic testing with 3 months or
  - CSF leak confirmed by clinical evaluation including physical exam within 3 months.
  - Incidence of all adverse events
  - CT evaluations of extradural collections
- Procedure: The neurological procedure and sutured dural repair was completed according to the standard practices of the investigator. Autologous pericranial, fascial, muscle or fat grafts were harvested to augment dural closure. Use of these materials was captured in the case report form. After the repair was completed, the patient was assessed for the intraoperative inclusion and exclusion criteria. If the patient met the criteria, a Valsalva to 20 cm H<sub>2</sub>O was completed to assess CSF leak. If the patient leaked, the quality (seepage or overt leak) was recorded and DuraSeal applied. The Valsalva was repeated and if a leak remained, a 2<sup>nd</sup> and final DuraSeal application was tried. Leakage after the 2<sup>nd</sup> application was recorded as a failure. Patient who did not meet the intraoperative criteria were considered screening failures and withdrawn from the study and not followed.
- Follow-up
  - Patients were examined at discharge or within 7 days post-op, at a 6 week post-op visit and at a 3 month post-op visit. These examination included:
    - Physical exam and vitals
    - Neurologic assessment
    - Lab test (renal function, hepatic function)
    - CT imaging (6 weeks and 3 months only)
    - Recording of concomitant medications
    - CSF leak evaluations
    - Wound healing assessment
    - Adverse events

### Study Results:

- Patient enrollment

Patients were considered enrolled when they signed informed consent. There were 132 patients consented for the study. All met the pre-operative criteria 111 patients met the intraoperative inclusion/exclusion criteria and were treated with DuraSeal. Twenty patients were excluded from the study based on intra-operative inclusion and exclusion criteria. These included 3 patients in whom the dural margin was less than 3 mm from the bony edge, 6 patients in whom non-autologous duraplasty materials were needed for dural closure, and seven patients in whom there was a gap of >2mm following primary dural closure. An additional six patients were excluded due to intra-operative finding of a pre-operative exclusion criterion. All 6 cases involved penetration of a sinus. One patient was excluded from the study despite meeting all criteria because the physician determined the patient was going to need an additional surgery within 2 weeks. The 111 treated patients represent the safety population for the analysis of the study data. Of the 111 patients who met all pre-operative and intra-operative inclusion and exclusion criteria, all 111 leaked either spontaneously or after Valsalva maneuver.

- Patient follow-up

The primary efficacy endpoint was recorded for all 111 patients treated with DuraSeal. Seven-day follow-up data is also available for all 111 treated patients. One patient died at 30 days, thus only 110 patients were available for the 6-week follow-up visit. An additional patient died at 85 days, making only 109 patients available for the final 90 day follow-up visit. Two patients did not participate in the 90-day visit, therefore 90-day data is presented on only 107 patients.

- Patient demographics

The mean age of the patients in the safety population (n=111) was 49.3 with a range of 20-75. Of the 111 patients, 68.5% were female and 29.7% were active smokers. Table 1 shows the various indications for surgery. 81% of the cases involved craniotomy and the other 19% craniectomy.

**Table 1**

Indication for Surgery	Number of patients (n=111)
AVM	7 (6.3%)
Aneurysm	12 (10.8%)
Chiari Malformation	6 (5.4%)
Cyst	3 (2.7%)
Epilepsy	10 (9.0%)
Nerve Decompression	21 (18.9%)
Tumor	51 (45.9%)
Acoustic	6
CPA mass	5
Dermoid/epidermoid	2
Frontal mass	5
Meningoma	12
Parietal/temporal	9
Other	12
P-com stenosis	1 (0.9%)

The most common indication for surgery was tumor resection (45.9%), and the most common surgical approach was suboccipital (41.4%). The population was evenly split between supra and infra-tentorial procedures (52.3% and 45.9%). Two patients had a combined supra and infra-tentorial approach.

- Primary Efficacy results

Out of the 111 treated patients, 67 (60%) had a spontaneous CSF leak after primary dural repair. The other 40% had a leak after Valsalva. Fifty patients had primary dural repairs that included autologous duraplasty materials including fascia (14.4%), muscle (21.6%), pericranium (10.9%), fat (2.7%) and other (1.8%). There were no patients excluded from the study due to a lack of leak with the Valsalva.

After the first application of DuraSeal, 105/111 subjects had no CSF leak with Valsalva. In 1 subject there was continued spontaneous leak after the first application and in 5 there was leak with Valsalva. These six subjects all underwent a second application of DuraSeal. There were no leaks after the 2<sup>nd</sup> application. The average pressure of the Valsalva maneuver was 21.4 cm H<sub>2</sub>O with a range of 10-40. There were four subjects that did not have Valsalva to the required 20 cm H<sub>2</sub>O after DuraSeal application. Two of these subjects had pressures of 18 and 19 cm H<sub>2</sub>O, and two had only 10 cm H<sub>2</sub>O. Excluding the 2 patients in which a pressure of only 10 was reached, there were 109 patients with no leak after *adequate* Valsalva (**109/111, 98.2%**).

- Safety
  - Device malfunctions

There were 13 cases in which the required gelation test was not performed due to device assembly errors. In these cases, a new kit was opened and all gelation tests were passed. There were two cases of device malfunction, both involved clogging of the y-connector which prevented precursor mixing and delivery. In both cases a new kit was obtained.

- Serious adverse events

There were a total of 54 serious adverse events reported in the 111 patients treated. These events occurred in 32 patients (28.8%). Surgical wound infections and CSF leaks are discussed in detail below. Other serious adverse events that occurred in greater than 1% of the patient are shown in table 2 below.

**Table 2**

<b>Event</b>	<b>Number of events</b>	<b>Number of patients (n=111)</b>
<b>Deep wound infection</b>	9	8
<b>Arrhythmia</b>	2	2
<b>Cerebral edema</b>	2	2
<b>CSF leak</b>	6	6
<b>Stroke/CVA</b>	4	4
<b>Hydrocephalus</b>	3	3
<b>Meningitis (aseptic)</b>	2	2
<b>Meningitis (bacterial)</b>	2	2
<b>Cognitive disturbance</b>	3	3
<b>Cranial nerve deficit</b>	2	2
<b>Motor deficit</b>	4	4
<b>Neuropsychiatric disorder</b>	2	2

- CSF leakage

CSF leak was defined as 1) a CSF leak or pseudomeningocele related surgical intervention (breaking the skin) within 3 months of the procedure; 2) CSF leak confirmed by diagnostic testing with 3 months of the procedure or 3) CSF leak confirmed by clinical evaluation including physical exam within 3 months post-op.

There were 5 cases (5/111, 4.5%) of protocol defined CSF leak in the safety population. Three of the patients had a pseudomeningocele and the other two incisional CSF leaks. There is one additional case of a CSF leak that was encountered during re-operative for a deep wound infection that is described in detail below. Including this event, the rate is 6/111 or 5.4%.

\_\_\_\_\_ underwent resection of a pineal meningioma from an occipital approach. The patient's history is significant for hydrocephalus diagnosed in August of 2003 that had resolved prior to inclusion in the study. After dural closure there was spontaneous,

overt CSF leak. One day after hospital discharge (post-op day 16) the patient was re-admitted through the ER due to wound dehiscence, purulent drainage, and CSF leak. The patient was taken to the OR two days later for removal of the bone flap and debridement of a deep infection. Fluid testing was positive for beta-transferrin confirming a CSF leak. The patient continued to leak after the procedure and was treated for hydrocephalus with a lumbar drain for one month. The drain was then removed and the patient discharged.

[redacted] underwent a retrosigmoid craniectomy for fenestration of a CPA. After dural closure there was seepage of CSF from the suture line only after Valsalva. Six days post-op the patient presented with a subgaleal fluid collection which was treated conservatively with decadron but then progressed to an incisional CSF leak by POD #8. The patient was treated with prophylactic antibiotics, additional sutures, a lumbar drain, an IVC catheter and eventually required a VP shunt. CSF cultures were positive for coagulase negative staph but only in the broth (most consistent with a skin contaminate, not an infection). In retrospect (and with examination of the patient's chart) he likely had hydrocephalus prior to the surgical procedure.

[redacted] underwent a sub-occipital craniectomy for an arachnoid cyst. There was spontaneous seepage of CSF from the suture line after dural closure. The patient presented on post-op day 20 with complaints of headache and localized swelling in the region of the incision. CT scan confirmed a pseudomeningocele. A permanent lumboperitoneal shunt was placed.

[redacted] underwent a supracerebellar, infratentorial craniotomy for a pineal region tumor. After sutured dural closure, there was seepage of CSF only with Valsalva. The patient presented on post-op day 28 with complaints of headache and focal swelling. A CT scan revealed a pseudomeningocele and a permanent lumboperitoneal shunt was placed.

[redacted] underwent a frontal craniotomy for a parasagittal meningioma. After dural closure there was spontaneous and overt CSF leakage. On post-op day eight a subgaleal fluid collection was noted. This was treated with a pressure dressing, admission to the hospital and aspiration. The collection persisted until the 3 month follow-up visit, and was therefore on-going at study exit.

There were two additional patients [redacted] with pseudomeningoceles that were treated with conservative therapy (no surgical intervention) that therefore did not meet the protocol definition of CSF leak. The CSF leak rate in the subgroup of supratentorial cases was 2/58 (3.4%) and infratentorial 5.7%.

- Infectious Complications

Wound complications included wound healing problems, hematoma, superficial infections and deep infections. Infections were classified based on the CDC criteria for each type. For superficial infections, this only includes those that occur within 30 days of

the surgery, but extends to 1 year post-op for deep infections in cases of a surgical implant.

Superficial Infections: Th [redacted] perfcial infection within 30 days of the procedure. This involved [redacted] who underwent a suboccipital craniectomy for Chiari malformation. She [redacted] ost-op day 7 with localized swelling and edema of the surgical wound. The patient was treated with antibiotics and debridement in plastic surgery clinic. The event resolved with no residual effects. The patient's wound was well healed at 3 months. There were three superficial infections after 30 days.

Deep wound infections:

There were eight deep wound infections reported by the sponsor (8/111, 7.2%). All 8 patients required an operative procedure for debridement and in six cases bone flap removal. The first case is [redacted] whose relevant clinical history is listed above under the CSF leak heading.

[redacted] underwent a frontal craniotomy for an AVM that originally presented with a subarachnoid hemorrhage. After a 10 hour procedure the patient awoke with left hemiparesis and decreased level of consciousness. CT scan revealed a hematoma which was treated conservatively. The patient was discharged on POD #21 and then presented to the hospital on POD #31 with fever and purulent drainage from the wound. She was taken to the OR for bone flap removal and debridement. After 25 days of IV antibiotics with continued fevers an exploratory procedure revealed vascular clips that had eroded through the dura. These were removed and the wound infection resolved.

[redacted] underwent a right parietal-occipital craniotomy for tumor. The patient was discharged 8 days post-op. She presented to her primary care physician 6 weeks post-op with a red, swollen wound. The wound had fluctuance and purulent drainage. The patient was taken to the OR for bone flap removal and debridement the next day and an EVD was placed. She was discharged 1 week later at which time the infection had completely resolved.

[redacted] underwent a suboccipital craniectomy and C1 laminectomy with duraplasty for Chiari malformation. Fives days post-op the patient presented to the ED with fever, headache and wound tenderness. Lumbar puncture showed high WBC count and antibiotics were started. Seven days later the patient's wound opened and a large amount of serosanguinous fluid was expressed. The patient was taken to the OR for debridement and a lumbar drain was placed due to a small amount of CSF leakage noted during the operation. There was no hole in the dura to repair per the operative report. The infection resolved with no residual effects.

[redacted] underwent a frontal-temporal craniotomy for a right pcom aneurysm. Forty-six days post-op the patient presented to clinic with copious brown drainage from the wound. He was admitted and underwent debridement but the bone flap was retained. The patient was treated with IV antibiotics. However on POD # 59 he presented with

worsening of the infection and recurrent drainage and was taken to the OR for bone flap removal. The infection resolved after this procedure and there were no residual deficits.

[redacted] underwent a suboccipital craniotomy for clipping of a left vertebral aneurysm. The patient experienced injury to cranial nerves 9 and 10 which necessitated a post-op feeding tube. On POD #15 the patient returned to clinic with headache, stiff neck and scant drainage from the wound. She was admitted and underwent debridement of the wound the following day. DuraSeal was removed at the time of this procedure. The sponsor reports the removal of the DuraSeal was responsible for a pseudomeningocele that appeared on POD #27 and was ongoing at 90 days. No additional information about this event is provided.

[redacted] underwent left partial-temporal craniotomy for aneurysm. The patient experienced a fever POD #1, cultures were negative and it resolved by discharge. At the 3 week post-op visit the wound was noted to be erythematous and draining. The patient was admitted and taken to the OR the following day for debridement. A central venous catheter was placed for long term IV antibiotics which the patient received until 3 month follow-up. There were no residual effects noted at 90 days.

[redacted] underwent a right temporal-parietal craniotomy for meningioma removal. At the 6 week post-operative visit the patients wound was noted to be erythematous. Two additional daily wound checks revealed the same and the patient was admitted and taken to the OR for debridement. Cultures were positive for gram-positive bacilli. The patient received IV antibiotics until the 90 day visit. At that time there were not residual effects noted.

#### Meningitis:

There were two cases of bacterial meningitis reported. The first was in [redacted] had a deep wound infection and is described above. The second was in [redacted] [redacted] and was diagnosed based on a CSF culture taken during the placement of a VP shunt of CSF leak. Multiple prior CSF samples taken during the patient's hospital course were negative. The patient had no documented symptoms of meningitis at the time and the condition resolved without residual effects.

#### **Adverse Event summary :**

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. There was one reported superficial infection, and three superficial infections that occurred after 30 days and were therefore excluded by CDC criteria. There was no control group with which to compare this rate of 8.1%. Meningitis is often included as a surgical infection in intradural surgery. Inclusion of the 2 cases of bacterial meningitis raises the overall surgical infection rate to 11/111 or 10%. Of the 9 patients with wound infections, there were 5 that had spontaneous CSF leaks in the OR after dural closure and 4 that only leaked with the provocative Valsalva

maneuver. The infection rate for patients with spontaneous CSF leaking intra-op was 7.4% (5/67) and for patients with a leak induced by Valsalva the rate was 9.1% (4/44)

The overall rate of CSF [redacted] reported by the sponsor was 4.5% (5/111). In one case of deep wound infection [redacted] there was a CSF leak noted at the time of the repeat surgery that necessitated the placement of a lumbar drain. This was not counted as a CSF leak in the sponsor's safety data, though the insertion of a lumbar drain would qualify as "a CSF leak or pseudomeningocele related surgical intervention (breaking the skin) 3 months of the procedure". This patient should therefore be counted. In [redacted] [redacted] a pseudomeningocele developed after removal of DuraSeal during the debridement. This event was noted in the section of CSF leaks as one of the pseudomeningoceles that was treated with conservative therapy that therefore did not meet the criteria to be counted as a CSF leak under the study protocol. However the patient level data in attachment 6-J indicates th [redacted] going at 3 months, and therefore not yet adequately treated. Including [redacted] who had the lumbar drain inserted, the rate of CSF leak was 5.4%. Out of these 6 patents, 4 had spontaneous leakage of CSF in the OR after dural closure, and 2 only leaked after a Valsalva maneuver. The rate of CSF leak rate in patients with spontaneous leaks intra-op (4/67, 5.9%) was not different from the rate in patients in whom a Valsalva was necessary to generate the intra-operative leak (2/44, 4.5%).

The rates of other serious adverse events shown in table 2 are comparable to the expected outcome of intracranial surgery. The majority of these events are unlikely to be related to the use of the device. In addition to infection and CSF leak, other events that could be related to the use of the device are those associated with excessive inflammatory response. These would include cerebral edema and aseptic meningitis. The rates of both of these events (1.8% for both) are low and consistent with the expected results in this population.

### **Comparison to the literature:**

The study design did not use a prospective control group, therefore, the adverse events captured must be compared to the neurosurgery literature to assess the safety of the device, and the risk benefit ratio.

Examination of the literature reveals a wide range of rates reported for surgical site infections. In the PMA the sponsor used the rate of 6.1% from the study on the DuraGen collagen dural substitute (3) for comparison purposes. The sponsor's rate of 8.1% is only slightly higher than this rate. However, in a paper published by Narotam PK et al (3) that provided results of the prospective study of DuraGen collagen dural replacement compared to sutured closure alone, they reported the same rate of 6.1% (28/459 cases) . This rate however included 141 contaminated and 72 clean-contaminated surgeries. These cases accounted for 21 of the 28 infections. In another study by Narotam and published in an earlier paper in 1994 (4) the relationship between the category of case (clean, vs clean contaminated, vs contaminated) and post-operative infection rates were examined. In this study of 2249 patients the rate of post-operative infection in clean cases

was 0.8% (when neural tube defects were excluded) compared to a rate of 6.0% in the cases of a foreign body placement and 9.7% for clean-contaminated cases. In the DuraGen study, the infection rate among clean cases only was 7/244 (2.8%). These clean cases can be further sub grouped into those with a foreign body implanted and those without. The infection rates were 3.2% in the foreign body group and 1.6% without.

The protocol for the DuraSeal study specified only clean cases, and contained an intra-operative exclusion criteria for cases in which a clean case became a clean-contaminated case (sinus penetration). Thus the final 111 treated cases in the presented data set contained only clean cases.

The clean-case infection rate of 1.6% reported in the DuraGen study (3) is consistent with several other prospective studies in the literature. Young et al in 1987 reported a prospective, randomized study of 846 clean neurosurgical procedures. The infection rate in patients receiving antibiotic prophylaxis was 0.96% compared to 3.6% without antibiotics. A sub-group analysis of craniotomy alone showed a 6.7% rate without antibiotics and 0% with (5). Bullock et al (6) also reported a prospective, randomized study of antibiotic prophylaxis in clean neurosurgical cases. In similar fashion to the DuraSeal study, patients in whom the air sinuses were breached were excluded from the final analysis. This study of 418 patients showed a 2.1% infection rate in the antibiotic treated group compared to 5.8% in the placebo group. In craniotomies, the infection rate in the antibiotic group was 1% (1/100). Djindjian found similar results in a prospective study of 356 patients with an infection rate of 0.6% in the antibiotic treated group (7). Finally, Pons et al studied ceftizoxime and vancomycin in a prospective, randomized study of antibiotic prophylactic use in consecutive neurosurgery cases (15). They reported a rate of primary infection (including superficial and deep wound infections, meningitis, cellulitis, abscess, osteomyelitis and stitch abscess) of 0.49% for cranial cases.

Slightly higher numbers were reported by Whitby et al in a study comparing trimethoprim/sulfamethoxazole to cefotaxime (8). They reported a wound infection rate of 2.5% in 630 patients. This however included shunt surgery (and 2 shunt infections). van Ek reported an infection rate of 3.3% in patient receiving antibiotics, and 10.3% in those without, but this study prospectively enrolled all patients undergoing craniotomy and did not specify only clean or elective procedures (9). Finally, Korinek et al published a large prospective analysis of 2944 craniotomy procedures to examine for risk factors for post-operative infection (10). Using a broad definition of infection that included wound infections and meningitis, she reports an overall infection rate of 4%. This study include emergency surgeries (617 cases), contaminated and dirty procedures (124 cases), and 964 cases in which antibiotic prophylaxis was not used.

In summary, the rate of wound infections in clean neurosurgical cases as best described by prospective studies in the literature ranges from 0-2% with craniotomies as having rates closer to 1%. Clean surgery without antibiotic prophylaxis raised the infection rate to 3-4%.

The literature on CSF leak rates in craniotomy cases is more varied. Reports in the literature show rates from 0-20% depending on the types of cases included in the study. The sponsor has provided multiple references of the CSF leak rates in acoustic neuroma surgery that show the rate in these cases ranges from 6% to > 20%. A meta-analysis that explored the rate of CSF leak after acoustic neuroma surgery found an average of 10.6% for the suboccipital approach. The sponsor points out that this is higher than upper bound of the 95% confidence interval for CSF leak in their study (8.4%). However, only 6 cases of the 111 in the sponsors study were acoustic neuroma resections. There are specific features of acoustic neuroma surgery (such as drilling of the petrous bone and exposure of air sinus during that drilling) that increase the risk of CSF leak in these cases compared to other posterior fossa surgery. Therefore one cannot extrapolate the rate of acoustics to other kinds of posterior fossa surgery or to craniotomy in general.

The rate of leak for a wider array of posterior fossa cases was reported by Roberti (11) as 13.6%, but this study included a majority of skull base approaches that involved bony drilling and/or exposure of air sinuses, thus a higher rate of leak is expected. The reports of the DuraGen study (3) showed a leak rate of 4.4% in the posterior fossa. This study examined the use of a dural substitute in patients in whom defects existed in the dura after primary closure. A study by Yoshimoto looked at 138 craniotomies for aneurysm (supratentorial) in whom a water tight dural closure was achieved with sutures alone (though no provocative Valsalva was used to test the closure). In this series there were no CSF leaks through the skin in any patient, though the rate of asymptomatic pseudomeningocele was 26% (12). There are several studies that examined CSF leak rates in a variety of intracranial cases (in a similar fashion to the DuraSeal study). These include a study of an off-label use of BioGlue to prevent CSF leaks that examined 216 craniotomies with a leak rate of only 2% (13). Another study by Kassam examined an off-label use of a fibrin glue, Tisseel, and found a 0% leak rate in cases with Tisseel and 5.5% without (14). In addition to the difficulty in finding a comparable population of patients for the one studied in the DuraSeal study, authors often use different criteria for diagnosing a CSF leak. In many cases only leaks that required surgical intervention are reported, and those treated with “conservative” measures were not included.

### **Summary:**

The sponsor successfully achieved a 98.2% rate of water tight closure as tested by a Valsalva to 20 cm after DuraSeal application. This is significantly greater than the 80% level selected as the definition for study success. The device seems effective at providing a water-tight dural closure in cases where suturing alone, or in combination with autologous grafting was not successful. The success criterion does correlate with the goals of a surgical closure of a craniotomy wound. However, since the benefits of a water tight closure are intuitive, but have not been shown in a well controlled study to lead to a clinical benefit for patients, the adverse event profile of the device must be carefully examined to determine what, if any, risks the device poses.

The wound infection rate (including both superficial and deep infections) of 8.1% (or 10% including meningitis) in the DuraSeal study is high compared to the literature, which in well controlled studies, shows the infection rate for clean craniotomies with the

use of antibiotic prophylaxis is about 1%. The subgroup of the DuraGen study that includes only clean craniotomies showed a rate of 1.6%. This raises the question of whether the DuraSeal may be a nidus for infection.

The CSF leak rate of 5.4% is within the wide range of rates reported in the literature. Unfortunately, given the variety of cases that were included in the study, finding comparable cases from the literature is challenging. These comparisons are further complicated by the varied definitions of what constitutes a CSF leak post-op in the literature. It is not possible therefore to make a valid comparison of the CSF leak rate encountered in this study with the literature.

The intent of the study design was to select patients at risk for post-operative CSF leak by only including patients that had an intraoperative leak either spontaneously or after a Valsalva to 20 cm H<sub>2</sub>O, which would mimic transient raises in intracranial pressure seen in normal physiologic conditions. However, in this study, all patients who met the inclusion and exclusion criteria leaked during the intra-operative testing. This suggests the population encompasses a more heterogeneous group of patients with respect to their CSF leak risk. However, the rate of post-op CSF leak in the spontaneous intra-op leak population (5.4%) was similar to the observed post-op CSF leak rate in the induced leak patients (4.5%).

The sponsor has been asked to respond to questions regarding the infection rate and CSF leak rate observed in this study. The responses to these deficiencies are discussed at the end of this document. These issues have been identified as draft panel questions for your consideration during your deliberations.

## STATISTICAL

The sponsor conducted a prospective, multi-centered, non-randomized, single-arm clinical study of 132 patients at 11 clinical sites (10 in U.S, and 1 in Europe). Of those, 111 met the intraoperative eligibility criteria and were treated with the DuralSeal Sealant. Of the treated patients, 107 (96.4%) completed the 3-month follow-up. Additional follow-up examinations were at discharge (usually 7 days) and 6-weeks. Two patients died due to causes related to their medical condition and 2 patients refused to return for follow-up visits and were, hence, lost. A patient was considered a success if there was no CSF leak from the dural repair intraoperatively after up to 2 applications of the DuralSeal Sealant, as tested by a Valsalva maneuver up to 20 cm H<sub>2</sub>O for 5-10 seconds.

The safety evaluation considered the occurrence of adverse events, clinical laboratory values, neurological assessments, and the occurrence of a CSF leak within 3-months post-operatively. Post-operative leaks were confirmed either by pseudomeningocele related surgical intervention, diagnostic testing (CT), or clinical evaluation. A summary of the data and results are provided in the clinical section of this memo.

### Comments

#### *Study Design and Follow-up*

Because of its simplistic design of a one-armed study, there were no issues of randomization or masking. Follow-up was also excellent. Being that the primary endpoint was intraoperative, there was 100% follow-up for this. As for post-operative leaks and safety, all of the 107 patients had their 3-month follow-up (excluding the 2 who died and 2 lost), and only one patient missed the 6-week visit. Thus, no “handling” of missing values was necessary.

#### *Pooling*

The sponsor provides a thorough justification for pooling across sites analysis. They tested for differences across sites for demographic characteristics (e.g., age, weight, smoking status), procedural characteristics (e.g., duration of surgery), and procedural outcomes (e.g., leaks/infection). Five of the sites had 10 to 23 patients; 4 sites with <3 patients were combined to form a pooled site; and the remaining 2 sites had 5 and 7 treated patients. Combining sites with just a few patients is not uncommon, provided the same protocol is followed, as was the case here. Although there were some statistical differences across sites with respect to patient demographic and procedural characteristics, “site” was not found to be predictive of any safety parameters.

#### *Statistical Methods*

At the study design phase, Confluent Surgical believed that their study success rate would be 90%. They convened a Neurological Advisory Board which came up with a minimally clinically acceptable success rate of 80%, to be used as an objective performance criterion or “OPC”. There was no “delta” built into this “OPC”, so that the lower limit of the 95% confidence interval would have to lie completely above 80%. Counting the 2 valsalva protocol deviations (only 10 cm H<sub>2</sub>O reached) as failures, the

success rate is 98.2%, with a lower bound of 93.6%. This is above the prespecified “OPC” of 80%.

Since the secondary endpoint of post-operative leaks at 3 months is also of interest, the post-operative leak rate counting the lost, and the dead as leaking, in an incrementing fashion was computed. The table below shows the results, with the first row reiterating the results as reported by the sponsor.

Incidence of Post-operative Leaks (3 months)			
Assumptions	[N=111 treated]	Post-op Leaks	Point Est. Upper 95% CI (2-sided)
Deaths & lost to follow-up are not leaking		5/111	4.5% 10.2%
Assume 2 lost would have post-op leak		7/111	6.3% 12.5%
Assume 2 lost & 2 deaths would have post-op leak		9/111	8.1% 14.8%

In a worst cases analysis, where one assumes the 2 lost and 2 deaths would have had a postoperative leak, the “true” post-operative leak rate could be as high as 14.8%.

### *Safety*

The sponsor reports the occurrence of adverse events mostly as descriptive statistics (i.e., counts, proportions). However, logistic regression was used to assess the impact of covariates on adverse events. It was found, for example, that current or past (= 10 yrs) smokers had 5 times the risk of developing an infection. The overall infection rate (9%), has been raised as an issue requiring additional information by the clinical reviewer. The post-operative leak rate was 4.5%, which was the same whether computed raw (5/111) or using Kaplan-Meier estimation which accounts for the post-operative losses and deaths. The sponsor claims the rate is below the literature rate of about 10%, although the confidence interval analysis shown in the above table shows that the true post-operative leak rate could be over 10%.

Deficiencies were noted in FDA's review of the sponsor's application. The deficiencies are provided here with the sponsor's answers reviewed per deficiency.

Deficiencies

- 1. The infection rate in the DuraSeal study (8.1% combined) is high compared to the evidence from the literature on the infection rates in clean craniotomy cases (e.g., 1.6% for the clean cases in the DuraGen study). Please address the following:**
  - a. The literature shows that the use of antibiotic prophylaxis impacts the infection rate. Please provide data about the use of antibiotics in DuraSeal cases including whether it was used in all cases and what antibiotics were used in each case, if available.**

The sponsor has provided a report detailing the antibiotic use in the trial. All patients received antibiotic prophylaxis. The most common antibiotic used was cefazolin, used in 91/111 patient. Other drugs used included vancomycin, cefuroxime, bacitracin, and cefepime. The infection rate in the DuraSeal study should therefore be compared to populations in the literature who received antibiotic prophylaxis.

- b. Without a control group, comparisons of adverse event rates must be made to the existing literature. The PMA states that the rate of 8.1% is comparable to the 6.1% rate seen in the DuraGen study. However, that study included contaminated and emergency cases; known to have high infection rates. Please provide a more complete comparison of wound infection rate to the available literature. This comparison should include examination of the types of cases included in studies cited as well as comparisons of other inclusion and exclusion criteria that have an impact on infection rates. Examination of the criteria used to establish the diagnosis of a surgical infection in both your study and the literature is also important.**

The sponsor has provided an additional analysis of the literature to respond to this deficiency. In the DuraGen study (Narotam, 1995) which has been cited as a comparison population for the sponsor's results, the criteria for classifying a case as "clean-contaminated" were the same criteria that Narotam, 1994, described in his prior study of risk factors for infection in neurosurgical cases. The criteria included cases in which the air sinuses were penetrated, cases involving fractures of the cranial base, and all cases lasting >2 hours. The infection rates for these various types of clean-contaminated cases from the initial study by Narotam, 1994, are shown in Table 3 below.

**Table 3 – Infection rates in Clean-contaminated cases (Narotam, et al. 1994)**

	<b>Entry into sinuses</b>	<b>Fracture of cranial base</b>	<b>Surgery 2-4 hours</b>	<b>Surgery &gt;4 hours</b>
<b># of cases</b>	30	15	178	23
<b># of infections</b>	2	2	10	3
<b>Infection rate</b>	6.7%	13.3%	5.6%	13.4%

In that same study, the infection rate in clean craniotomy was 0.8%. Therefore, cases lasting longer than 2 hours did have a higher infection rate than seen in clean cases. It is important to note that the difference between the cases lasting 2-4 hours and those lasting >4 hours while numerically large (6.5 vs 13.4%), was not statistically significant. For the sake of comparison, the sponsor provided a breakdown of the cases in the DuraSeal study by length of surgery. Sixty cases (54.1%) were 2-4 hours in length, and 42 (37.8%) were greater than 4 hours. Thus 102/111 cases would be classified as clean-contaminated by the Narotam classification (>2 hours), based on length of surgery. Comparisons of the results of the DuraGen study (Narotam, 1995) to those seen in the DuraSeal study are shown in Table 4 below.

As can be seen from Table 4, in the DuraGen Study (Narotam, 1995) an additional classification of “clean with foreign body” has been added. In the PMA study, the sponsor did not keep track of foreign objects implanted (such as titanium plates, cranioplasty cement, etc) and thus this classification cannot be assessed in the DuraSeal study. The sponsor notes that many of the study investigators routinely used some implants such as titanium plates. It is important to note that the difference in infection rate in the clean-contaminated class between the DuraGen control and treatment groups was not statistically significant. The infection rate in the DuraSeal clean-contaminated subpopulation was similar to the rate in the DuraGen treatment group.

**Table 4 Comparison of infection rates; DuraSeal study and DuraGen study**

Case type	DuraGen control	DuraGen collagen	DuraSeal
Clean	7/240 (2.9%)	1/62 (1.6%)	0/7 (0%)
Clean with foreign body	13/209 (6.2%)	6/182 (3.2%)	n/a
Clean/contaminated	4/91 (4.3%)	9/74 (12.0%)	12/102 (11.8%)
<b>Total</b>	24/540 (4.4%)	16/318 (5.0%)	12/111 (10.8%)

The sponsor also reports that ASA (American Society of Anesthesiology) score > 2 has also been reported in the literature to be a risk factor for surgical wound infection. In the study by Korinek et al, the authors examined 2900 neurosurgical cases and found ASA score > 2 to be a significant risk factor for post-op infection. 33% of the cases in the DuraSeal study had an ASA score >2.

The sponsor conducted uni and multi-variate analyses of factors possibly associated with infections in patients treated with DuraSeal. With a univariate analysis, the sponsor found that the duration of surgery, the amount of DuraSeal used, the use of an intraoperative shunt and smoking status appeared correlated with infection. Only smoking status was found to be correlated with infection using multivariate analysis.

Finally, the sponsor provides a table (table 3 of the amendment) comparing the results of the DuraSeal study to reported literature on duraplasty materials. The infection rates in these studies varied from 2.97% to 15.0%. The sponsor points out that these studies included predominately clean cases, the definition of infection was often not listed, or only deep wound infections were considered, and that follow-up was often low (75% in one example). The sponsor concludes that the infection rate in the DuraSeal study (8.2%, with a C.I of 3.8-14.8%) is similar to the rates seen for other series of craniotomies published in the literature, and to the rates seen in studies of duraplasty materials.

The cases included in the DuraSeal study involved clean (by the CDC and protocol definitions), elective craniotomies. However, there was a substantial number of high risk patients (ASA >2) and an overwhelming majority (>90%) of cases longer than 2 hours, with 38% greater than 4 hours. While these long cases would be classified as “clean-contaminated” by the Narotam (1994) classification, which has been used in the neurosurgical literature, the other types of clean-contaminated cases (sinus penetration and skull base fractures, transoral or transsphenoidal approaches) were excluded from the DuraSeal study. Therefore the population included is unique from those reported in the literature. The subgroup analysis of several large literature studies including Narotam

(1995) support that patients who undergo procedures longer than 2 hours have a higher infection rate than seen in truly “clean” cases, however one cannot make statistically valid comparisons based solely on these subgroup analyses. The infection rates reported in studies of somewhat similar cases to those included in the DuraSeal study seem to fall within the confidence interval (3.8-14.8%) of the rate reported in the DuraSeal study. None of the reported articles however uses inclusion and exclusion criteria that result in a population with the same risk profile as the DuraSeal population.

2. **The rate of CSF leak for intradural craniotomy in the literature varies from 0-22% depending on the types of cases studied. Acoustic neuroma surgery is particularly prone to this complication. The comparison of the rate of leak seen in the DuraSeal study to those found in a meta-analysis of surgery for acoustic neuromas is therefore flawed.**
  - a. **Please provide a comparison from the literature of CSF leak rates in cases similar to the ones included in this study. Particular attention should be given to the differences in inclusion and exclusion criteria for both the DuraSeal study and the selected literature that predict high risk of CSF leaks.**
  - b. **[redacted] who had a lumbar drain inserted to treat a CSF leak encountered during a revision surgery should be included in the overall CSF leak rate. Please revise the adverse events description to include this case and give 95% confidence intervals for these revised numbers.**

The sponsor has included [redacted] as a CSF leak and has updated all the adverse event data tables to include [redacted] the overall CSF leak rate is 5.4% In infratentorial cases, the rate is 7.5% (4/53) and 3.4% (2/58) for supratentorial cases.

In response to part a. the sponsor has provided a review of the literature. They identify 3 prospective studies with which to make comparisons. There are numerous retrospective reviews published, however the follow-up rates, definitions of CSF leak and biases due to the retrospective design make these less ideal for comparison.

The first study by Kumar is a study of BioGlue, a synthetic adhesive used to augment dural closure, much like DuraSeal. This product is not legally marketed in the US for this use. The study includes both intra and supratentorial craniotomies with a similar mix of cases as seen in the DuraSeal study (though with a slightly higher rate of supratentorial cases). The specific definition of CSF leak was not given, but the only described cases are of actual CSF fistula. Additionally, follow-up was limited to one visit at 6 weeks. The leak rate was 1.2% (2/167). The sponsor compares this to the rate of CSF fistula in the DuraSeal study (2/111, 1.8%).

The second prospective study was by Bejjani et al and reports on an IDE study of DuraSIS, a cleared dural substitute. This study of 51 patients reported a CSF leak rate of 2% (1/51 cases). There was also an imaging evaluation of 26 patients that revealed 1 pseudomeningocele (4% of studied patients). The definition of CSF leak was not given in the article, and patient follow-up was limited to 10 days or less in 20% of the patients.

The final prospective study is reported by von Wild et al., and it a study of DuraPatch in 101 patients. This study included both supra and infratentorial craniotomies (75% supratentorial) and excluded cases that involved the frontal sinus and frontal skull base. A clinical diagnosis of CSF leak was used (not just CSF fistula). The CSF leak rate was 12.9% in this series. This study did not, however, exclude air sinus penetration (other than the frontal sinus) cases. Penetration of the mastoid air cells is a risk factor for CSF leak, and these cases were excluded from the DuraSeal study. The von Wild study also included only patients with dural defects that could not be closed and required a patch. The risk of leak in these cases requiring a patch is different (and likely higher) than for cases where a sutured dural closure is possible.

The sponsor includes comparisons to several retrospective reviews as well. One example was a study by Sawamura et al. that examined the use of aerosolized fibrin glue in supratentorial elective craniotomies. Cases involving the cranial base, the mastoid bone and posterior fossa were excluded. The definition of CSF leak was not explicitly given and was diagnosed by a retrospective review of the patients' charts. There was a post-op CSF leak rate of 3.1% in the aerosolized fibrin glue group and 8.9% in the control group. This was compared to the CSF leak rate of 3.4% in supratentorial craniotomies in the DuraSeal study. The Sawamura study did not exclude cases involving the air sinuses, and in fact 2 cases of CSF rhinorrhea were encountered in patients with surgery involving the frontal sinus. These cases would have been excluded from the DuraSeal study.

Comparisons of the CSF leak rate in the DuraSeal study to the literature is challenging due to the differences in the risk factors for leak between these various populations of patients. In the above listed prospective studies, two had rates that were numerically lower than the DuraSeal study (Kumar and Bejjani), though the definition of CSF leak and the adequacy of the follow-up period for both of these studies is not clear from the published report. In the third prospective study (von Wild), the CSF leak rate was higher than the DuraSeal rate, but the population appears to include cases at higher risk. The same issues arise with the retrospective reviews, which are further compounded by biases involved with retrospective examinations.

- 3. The study effectiveness pass/fail criterion chosen for the intraoperative surrogate endpoint was specified to be 80% successes, or 80% of patients sealed as indicated by the Valsalva test, as recommended by Confluent Surgical’s Neurological Advisory Board panel. Please note that this pass-fail criterion does not meet our current usage of an “objective performance criterion” in clinical trial study. Please provide information that supports this value for the pass/fail criterion as a clinically meaningful specification, i.e., information that supports the clinical benefit of the 80% rate of patients without CSF leaks in your study.**

The sponsor indicated that the 80% success criterion was justified based on the following concepts:

- Leakage of CSF into the extradural space is due to lack of a watertight sutured dural repair. Pinholes produced by surgical needles provide a pathway through which CSF can leak out.
- Persistent CSF leakage is associated with pain, low-pressure headaches, wound dehiscence requiring surgical intervention, infection and meningitis. Achieving watertight dural closure is considered, by some, to be a basic neurosurgical tenet.
- Due to concerns of post-operative CSF leaks, surgeons use a variety of biomaterials that have not been approved as dural sealants, e.g., Surgicel, Gelfoam, cyanoacrylate glues and fibrin glue.
- Confluent’s neurological advisory board “indicated that if the DuraSeal Sealant was able to provide ‘watertight’ closure in 80% of patients that demonstrated intraoperative CSF leakage after completion of sutured dural repair, it would be an important advance in achieving watertight dural closure and the device would provide a useful tool that they currently lack.”
- The 80% criterion was based on a study by Yoshimoto et al wherein the investigators determined, via CT images, that 74% of patients treated with fibrin glue did not have extradural fluid collection whereas only 58% of patients not treated did not have extradural fluid collection. Therefore the sponsor was attempting to compare themselves against the effectiveness of fibrin glue by using the 80% value as their objective performance criterion.
- The sponsor asserts that the 80% success criterion is greater than or consistent with the achieved success rates reported for surgical sealants approved for use as adjuncts to standard surgical techniques to prevent fluid leakage during vascular repair. “For example, the BioGlue Surgical Adhesive (Cryolife Inc.: P010003) is indicated for use as an adjunct to standard methods, such as sutures, for achieving hemostasis during repair of large vessels. In the BioGlue study, hemostasis success was achieved in 61% of patients treated. CoSeal Surgical Sealant (Cohesion Technologies, Inc.: P010022, a PEG-based sealant) was evaluated in a study to assess safety and effectiveness of the sealant to seal anastomotic suture lines in patients undergoing placement of vascular grafts. In the CoSeal study, success was achieved in 81% of patients treated.”

- Similar to the DuraSeal study, safety and effectiveness endpoints of the vascular sealant products were established based upon an intraoperative sealing endpoint. “Use of an intraoperative endpoint is justified for assessment of primary effectiveness of surgical sealants as other patient factors and comorbidities may confound the ability to assess device effectiveness on a longer term basis (e.g., development of hematologic dyscrasias and coagulopathies following vascular procedures leading to hemorrhage or tumor progression and development of post-operative hydrocephalus in cranial procedures resulting in CSF leaks.)”

The vascular sealant studies were reviewed and it was found that the devices achieved hemostatic ‘closure’ of the vascular sites as reported by the sponsor. The sponsor’s response adequately identifies information that indicates why they believed the 80% criterion was clinically meaningful.

- 4. Your inclusion criteria and success criteria refer to the presence or absence of a CSF leak upon Valsalva maneuver “up to 20 cm H<sub>2</sub>O for 5-10 seconds”. Please explain why 4 patients at Site [redacted] achieved a pressure of 30-40 cm H<sub>2</sub>O, and why, for two of these patients ([redacted]) the post-treatment testing pressure was 5-10 cm less than the**

The sponsor mentions that the Valsalva maneuver does not always provide exact measurements. The Valsalva measurements are accurately documented and these patients simply represent protocol deviations. With respect to the 2 patients that did not reach the protocol-defined ‘20 cm H<sub>2</sub>O for 5-10 seconds’ criterion, the sponsor has agreed to treat them as failures (see response to deficiency #6).

- 5. You claim that there were 132 patients enrolled, and 20 intraoperative screening failures plus 1 exclusion due to the necessity of a second procedure, resulting in 111 treated with DuraSeal. Please explain why the patient numbering system (as shown in Volume 5, Listing 14, for example) has many more gaps than would account for [redacted] patients not treated. For example, 14 patients were enrolled at [redacted] treated, yet the patient ID’s range from 2 to 53. We need this information to understand your patient accounting.**

Sequential patient numbering was done at the time of screening. Not all patients screened and assigned an identification number were enrolled in the study. As patients were determined to be ineligible on the basis of not meeting preoperative criteria, the corresponding patient identification number became obsolete. Patients that were determined to be eligible to participate in the study retained their original identification number assigned at screening. A table listing all patients screened and enrolled was provided. A review of the listings indicates that the exclusions were due to protocol rules.

- 6. Two subjects did not have adequate Valsalva maneuvers after DuraSeal application (pressure was only raised to 10 cm), as noted above. These two subjects should not be counted as successes. Please revise the primary efficacy data and confidence intervals to indicate the success rate without these two cases.**

The sponsor agreed not to include the patient in the Intent-to-Treat determination of the primary efficacy endpoint, i.e., intra-operative assessment of CSF leakage. Therefore, instead of 100% success, the device was successful in 98.2% of patients treated with the 95% confidence interval from 93.6% to 99.8%. The device still surpasses the 80% objective performance criterion.