SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Sealant, Dural

Device Trade Name: Adherus® AutoSpray Dural Sealant

Device Procode: NQR

Applicant's Name and Address: HyperBranch Medical Technology, Inc.
800-12 Capitola Drive
Durham, North Carolina 27713
USA

Date(s) of Panel Recommendation: N/A

Premarket Approval Application (PMA) Number: P130014

Date of FDA Notice of Approval: March 30, 2015

Priority Review: N/A

II. INDICATIONS FOR USE

Adherus® AutoSpray Dural Sealant is indicated for use in patients 13 years of age and older, as an adjunct to standard methods of dural repair, such as sutures, to provide watertight closure during cranial procedures.

III. CONTRAINDICATIONS

Adherus® AutoSpray Dural Sealant should not be used in confined anatomical spaces where nerve compression is of concern. The hydrogel may swell by up to 13% of its size in any dimension or 46% by volume after application.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Adherus® AutoSpray Dural Sealant labeling.

V. DEVICE DESCRIPTION

Hydrogel:

The Adherus® AutoSpray Dural Sealant is a surgical sealant that polymerizes to form a hydrogel film when sprayed onto the surgical site. The Adherus® AutoSpray Dural

Sealant system consists of components for preparation of a completely synthetic, absorbable sealant and a pre-assembled applicator for delivery of the sealant to the target site. The Adherus® AutoSpray Dural Sealant is composed of two solutions, a polyethylene glycol (PEG) ester solution and a polyethylenimine (PEI) solution (referred to as the "green" and "clear" precursors, respectively). When mixed together, the precursors cross-link and form the surgical sealant. The mixing of the sealant precursors is accomplished within the tip of the applicator. The Adherus® AutoSpray Dural Sealant is absorbed over approximately 90 days, allowing time for the dural surface to heal.

Applicator:

The Adherus® AutoSpray Dural Sealant Applicator is a sterile, single-use electromechanical, battery operated device with internal system components that provide air flow to aid in the delivery of a synthetic, absorbable two-component hydrogel sealant system. The device is supplied as a pre-assembled applicator and two separate glass vials, one of which is packaged within a foil pouch (see Figure 1). The Adherus® AutoSpray Applicator is comprised of the following primary components:

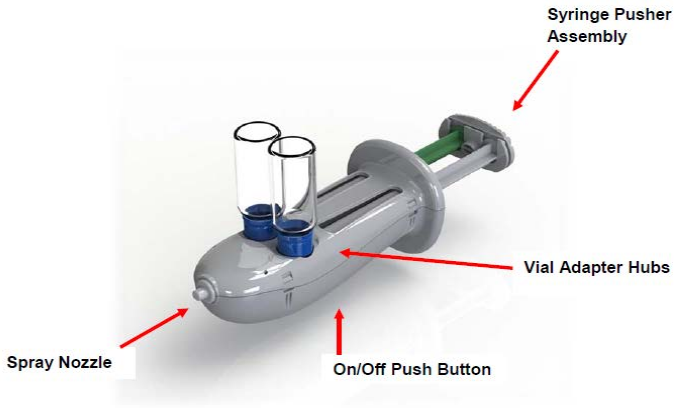


Figure 1: Adherus® AutoSpray Dural Sealant Applicator

Spray Nozzle:

The spray nozzle thoroughly mixes the two reconstituted solutions and delivers the mixed solution to the target site through a tight spray pattern. The spray nozzle is attached to the system and is not removable.

Vial Adapter Hubs:

On the top of the housing, the vial adapter hubs accept the vials containing the crosslinking components of the Adherus® AutoSpray Dural Sealant. During the reconstitution phase, the vials are attached to the vial adapter hubs. After reconstitution is completed, the hubs are removed from the AutoSpray by rotating them counter-clockwise. Removing the hubs opens the pathways for the solutions to flow through the nozzle.

On/Off Push Button Switch:

On the other side of the housing is the On/Off switch, which turns the battery operated air pump on and off. The device is shipped with the switch in the OFF position, which isolates the air pump from the battery power source. At the time of formulation delivery, the switch is depressed, putting the switch into the ON position and turning on the air pump.

Battery Removal Door:

On the underside of the housing, is a door which allows the Operating Room (OR) staff to remove the batteries (two AAA) for separate disposal after the device is used, if necessary. The battery door is glued shut. A flat instrument can be used to pry the battery door open and remove the batteries for disposal.

Syringe Pusher Assembly:

The syringe pusher assembly mechanically locks the two syringe plungers such that advancement of both syringe plungers occurs simultaneously.

The operating procedure for the Adherus® AutoSpray Dural Sealant can be found in the Instructions for Use.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of the dura to provide watertight closure during cranial procedures: application of sutures, use of dural replacement materials (duraplasty) for covering significant dural gaps, adhesives, and hemostatic agents. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

In addition, there are many dural repair techniques that serve to augment suture repair. These involve the local application of biological adhesives[1] such as fibrin glue and BioGlue™[2], absorbable gelatin or collagen sponge, autologous muscle, temporalis fascia, fascia lata, pericranium ligamentum nuchae, fat grafts, cadaveric human dura mater, bovine pericardium, cyanoacrylate glue, and hydrogels[3,4].

VII. MARKETING HISTORY

The Adherus® AutoSpray Dural Sealant obtained CE Mark and has been commercially available in the European Union since May 16, 2012. The Adherus® Dural Sealant, which employs a commercially available applicator rather than the AutoSpray applicator, obtained CE Mark in May 2009. In addition, the product is commercially available in the following countries: Western European Countries (2010), South Africa (2010), Israel (2010), United Arab Emirates (2011), Turkey (2011), Malaysia (2011), Argentina (2011),

Brazil (2011), Peru (2011), Saudi Arabia (2012), and Australia (2013). Neither the Adherus® AutoSpray Dural Sealant nor the original Adherus® Dural Sealant has been withdrawn in any country due to reasons related to the safety or effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device (occurring at a rate of ≥ 1%). The Adherus® AutoSpray Dural Sealant was evaluated in 124 investigational subjects in the pivotal clinical study. The adverse event rates presented are based on the number of subjects having at least one occurrence of a particular adverse event divided by the total number of subjects treated. The incidence and nature of adverse events observed in this study are consistent with the type and complexity of the neurosurgery performed and the co-morbid state of the treated subjects. There were 4 deaths. The deaths were attributed to the subjects' prior condition.

Table 1: Adverse Events Occurring at a Rate of ≥ 1% of Adherus® AutoSpray Dural Sealant Treated Patients

Adverse Event	Patients (n (%)) N=124
Anaemia	**3 (2.4)**
Leukocytosis	**2 (1.6)**
Deafness Unilateral	**2 (1.6)**
Tinnitus	**4 (3.2)**
Diplopia	**5 (4.0)**
Eyelid Ptosis	**2 (1.6)**
Periorbital Oedema	**6 (4.8)**
Vision Blurred	**7 (5.6)**
Dysphagia	**4 (3.2)**
Nausea	**2 (1.6)**
Adverse Reaction	**6 (4.8)**
Chest Pain	**3 (2.4)**
Disease Progression	**3 (2.4)**
Fatigue	**2 (1.6)**
Pneumonia	**2 (1.6)**
Urinary Tract Infection	**2 (1.6)**
Wound Infection	**2 (1.6)**
Incision Site Hypoaesthesia	**3 (2.4)**
Incision Site Pain	**4 (3.2)**
Periorbital Haemorrhage	**3 (2.4)**
Post Procedural Oedema	**2 (1.6)**
Pseudomeningocele	**9 (7.3)**
Seroma	**3 (2.4)**
Subdural Haematoma	**3 (2.4)**
Wound Dehiscence	**2 (1.6)**

Muscular Weakness	**2 (1.6)**
Aphasia	**4 (3.2)**
Balance Disorder	**2 (1.6)**
Convulsion	**5 (4.0)**
Cranial Nerve Palsies Multiple	**2 (1.6)**
Dizziness	**7 (5.6)**
Embolic Stroke	**2 (1.6)**
Headache	**14 (11.3)**
Hemiparesis	**2 (1.6)**
Hypoaesthesia	**4 (3.2)**
Hypoglossal Nerve Paralysis	**2 (1.6)**
Memory Impairment	**2 (1.6)**
Nystagmus	**3 (2.4)**
Paraesthesia	**5 (4.0)**
Sensory Loss	**3 (2.4)**
Tremor	**2 (1.6)**
VIIth Nerve Paralysis	**3 (2.4)**
Vocal Cord Paralysis	**2 (1.6)**
Atelectasis	**2 (1.6)**
Respiratory Failure	**2 (1.6)**
Alopecia	**2 (1.6)**
Rash	**2 (1.6)**
Swelling Face	**4 (3.2)**

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

In Vitro (Bench) Testing:

In vitro (bench) testing has been performed to evaluate the safety and effectiveness of the Adherus® AutoSpray Dural Sealant and the Adherus® AutoSpray Applicator. Tables 2 and 3 summarize the tests and results for the dural sealant and the Adherus® AutoSpray Applicator, respectively.

Table 2: In Vitro Testing - Adherus® AutoSpray Dural Sealant

Verification Test	Purpose	Specifications	Results
Young's Modulus	Mechanical test to evaluate the flexibility of the material	Young's modulus between 70 – 190 kPa.	Pass
Swelling Capacity	Evaluates the percent weight gain resulting after a 24-hour immersion of the hydrogel in 37° C phosphate buffered saline (PBS) at a pH of 7.4.	Gravimetric swelling ≤ 46%.	Pass
Burst Strength	Evaluates the strength of the surgical sealant when placed over a 3 mm diameter defect (hole) formed in a collagen sausage casing material. Once cured, the specimen is placed into a fixture and liquid is pressurized behind the tissue of the casing in order to determine the pressure needed to rupture the repair.	Burst strength (pressure) ≥ 80 cm H_2O.	Pass
Gel Set Time	Test evaluates the time it takes from application of the liquid formulation to formation of a hydrogel as measured by manual manipulation.	Gel set time ≤ 3 seconds	Pass

Table 3: In Vitro Testing - Adherus® AutoSpray Applicator

Verification Test	Purpose	Results
Audible Noise	Evaluates the decibel measurement of the activated device.	The decibel level is < 75 dB.
Battery Life	Evaluates the amount of time the device will function.	The device will function for a minimum of 2 hours of continuous use.
Water Spillage	Determines whether the device will continue delivery during and after a water leak.	Complies with the requirements set forth in IEC 60601-1 for spillage and leakage
IEC 60601-1 Medical Electrical Equipment Part 1: General requirement for basic safety and essential performance IEC 60601-1-2 (ed.3):2007-Medical Electrical Equipment Part 1-2: General requirements for safety-Collateral Standard : Electromagnetic compatibility-Requirements and tests	Certifies that documented builds of Adherus AutoSpray applicators are in compliance with IEC 60601-1 and IEC 60601-1-2 standards.	The AutoSpray Applicator complies with the standards.

Biocompatibility Testing:

The Adherus® AutoSpray Dural Sealant has been identified as a tissue/bone contacting permanent implant. Biocompatibility testing of the hydrogel has been performed in accordance with FDA's Blue Book Memorandum G95-1 and EN ISO-10993, "Biological Evaluation of Medical Devices Part 1." The initial series of tests was conducted on the Adherus® Dural Sealant delivered by the Nordson Micromedics Gas-Assisted Applicator (Table 4). During product development, a design change was made, and the new applicator was called the AutoSpray Applicator. Cytotoxicity, irritation, systemic toxicity, genotoxicity, and hemolytic potential of the Adherus® Dural Sealant as delivered by the AutoSpray Applicator were tested (Table 5). No additional biocompatibility safety concerns were raised as a result of the original evaluation or updated biocompatibility evaluation of the Adherus® AutoSpray Dural Sealant.

Table 4: Summary of Biocompatibility Testing Conducted on Adherus® Dural Sealant Delivered with Nordson Micromedics Applicator

Test	Description of Test Performed/Test Sample Extraction Conditions	Ref. Standard	Results
Cytotoxicity	ISO Agarose Overlay method using L929 Mouse Fibroblast Cells Saline (0.9%); 37ºC / 72 hrs	ISO 10993-5	Test article considered non-cytotoxic.
Irritation/Intracutaneous Reactivity	Intracutaneous Injection Test-ISO (reactivity for Irritation and delayed-type hypersensitivity) Saline (0.9%); 37ºC / 72 hrs	ISO 10993-10	Test article is considered a negligible irritant.
Systemic Toxicity (acute)	Systemic Injection Test-ISO Saline (0.9%); 37ºC / 72 hrs	ISO 10993-11	Test considered negative.
Sensitization	Murine Local Lymph Node Assay for delayed contact sensitization Saline (0.9%); 37º C / 72 hrs	ISO 10993-10	Test article is not considered a sensitizing agent.
Hemolysis	In-vitro Hemolysis Saline (0.9%); 37ºC /72 hrs	ISO 10993-4	Test article considered non-hemolytic.
Genotoxicity	Bacterial Reverse Mutation Study Saline (0.9%), 37ºC / 72 hours	ISO 10993-3	Test article is not considered to be mutagenic.
	Chromosomal Aberration Assay Saline (0.9%); 37ºC / 72 hrs	ISO 10993-3	Test article did not induce chromosomal aberrations and is considered non-clastogenic.
	Mouse peripheral blood micronucleus study. Saline (0.9%); 37ºC / 72 hrs	ISO 10993-3	Test article is considered non-mutagenic.
Intramuscular Implantation Study	ISO Intramuscular Implantation Study (two week); no extract – direct implantation	ISO 10993-6	Test article is considered a non-irritant.

Test	Description of Test Performed/Test Sample Extraction Conditions	Ref. Standard	Results
Subcutaneous Implantation Study	ISO Subcutaneous Implantation Study (10 day); no extract – direct Implantation.	ISO 10993-6	Test article does not demonstrate any remarkable difference to the control. Bioreactivity Rating of 0.0 -- No Reaction).
Subchronic Toxicity	13 Week Systemic Toxicity in Rabbits; subcutaneous implantation to evaluate potential subchronic systemic toxicity.	ISO 10993-11	Test article considered a non-irritant with no systemic toxicological observations noted.
13 Week Neurotoxicity Study	Thirteen Week Neurotoxicity Study of Adherus Dural Sealant following parenchymal Implantation in Albino Rats.	GLP Study (21 CFR Part 58)	No changes evident (brain or spinal cord away from implant site).
Subcutaneous Implantation – Biodegradation Study	Subcutaneous Implantation of Hydrogel Film in Rats for Absorbable/Resorbable Material In Vivo Biodegradation Rate Assay.	GLP Study (21 CFR Part 58)	No microscopic detection of Adherus Dural Sealant at 12 weeks.
2 Week Neurotoxicity Study	Two Week Neurotoxicity Study of Adherus Dural Sealant Extracts after Injection into the Lateral Cerebral Ventricle or Cisterna Magna in Albino Rats.	GLP Study (21 CFR Part 58)	Test Article was well tolerated (no gross or microscopic lesions different from control).

Table 5: Summary of Biocompatibility Testing Conducted on Adherus® AutoSpray Dural Sealant Delivered with AutoSpray Applicator

Test	Description of Test Performed/Test Sample Extraction Conditions	Ref. Standard	Results
Cytotoxicity	ISO Agarose Overlay using L-929 Mouse Fibroblast Cells Cottonseed Oil; 37ºC / 72 hrs	ISO 10993-5	Test article is considered non-cytotoxic
Cytotoxicity	ISO Agarose Overlay using L-929 Mouse Fibroblast Cells normal saline; 37ºC / 72 hrs	ISO 10993-5	Test article is considered non-cytotoxic
Intramuscular Implant Test	2-week Duration Rabbit Model	ISO 10993-6	The test article is considered a non-irritant.
Intracutaneous Reactivity Test	ISO Intracutaneous reactivity for Irritation and delayed-type hypersensitivity normal saline; 37ºC / 72 hrs	ISO 10993-10	Requirements met by test article
Systemic Toxicity (acute)	ISO Systemic Toxicity Study normal saline; 37ºC / 72 hrs	ISO 10993-11	The test is considered negative

Test	Description of Test Performed/Test Sample Extraction Conditions	Ref. Standard	Results
Hemolysis – Human Blood	Normal saline; 37ºC / 72 hrs	ASTM Guideline F-756-08	The test article is considered non-hemolytic
Bacterial Mutagenicity Test – Ames Assay	Normal saline; 37ºC / 72 hrs	ISO 10993-3	The test article is considered non-mutagenic.

B. Animal Studies

A series of animal studies were conducted to evaluate the in vivo performance and safety of the Adherus® AutoSpray Dural Sealant. Table 6 provides a summary of the animal tests performed and the relevant findings.

Table 6: Summary of Animal Studies

Test Performed	# of Animals Duration of Study	Summary/Relevant Findings
Canine Durotomy Repair Model	2 Canine 3 Weeks	Study performed to evaluate the appearance and endurance of an Adherus Surgical Sealant when used as an adjunct to dural closure in a canine durotomy repair model. Both animals had an approximate 3 cm x 2 cm bone flap removed from the left frontoparietal region of the skull. An approximate 2 cm incision was made through the dura and the arachnoid so that Cerebral Spinal Fluid (CSF) was allowed to freely egress. Once leakage was verified, the dura was loosely approximated with 6-0 nylon suture leaving an approximate 2 mm gap. The incision was blotted dry and the sealant was applied to a depth of 1-2 mm. The durotomy site was tested for CSF leakage with a Valsalva maneuver up to 20 cm H_2O (15 mm of Hg). No CSF leakage occurred. Neither animal experienced test article related clinical signs following surgery. The test article was well-tolerated by the animals and produced no histopathological changes in the brain or surrounding tissue. The incisions, when pressure tested at two and three weeks post administration, revealed no leakage of CSF at sustained intracranial pressures, induced with a saline infusion, in excess of 105 cm of H_2O (77 mm Hg). MRI scans demonstrated that the surgical sealant was visible in all images (T2, FLAIR, T1, and T1 with contrast) immediately following surgery and at 2 weeks and 3 weeks post-surgery.

Test Performed	# of Animals Duration of Study	Summary/Relevant Findings
Canine Craniotomy Model	15 Canine ●8 Test ●7 Control 6 Months	Study performed to evaluate the safety, effectiveness, and degradation profile of Adherus AutoSpray Dural Sealant as a tissue sealant in canine durotomy repair. After an approximate 2 cm incision was made through the dura and the arachnoid so that CSF was allowed to freely egress, the dura was loosely approximated with 6-0 nylon suture leaving a gap of approximately 2 mm. In the treated animals, the sealant was applied to the dural repair to a depth of approximately 1.0 mm and was subsequently tested for CSF leaks with a Valsalva maneuver up to 20 cm H_2O. In the control animals CSF leaks were verified by a Valsalva maneuver up to 20 cm H_2O (no surgical sealant was applied). The results show that none of the treated animals experienced test article related clinical signs following surgery. There were no intra-operative CSF leaks after one application of the sealant. This sealing effectiveness was carried over to the post-operative period in which all of the treated animals at one week and six months continued to experience no CSF leaks, even with a saline infusion which raised the intracranial pressure (ICP) to approximately 65 cm H_2O. A series of MRI scans demonstrated that the surgical sealant was visible in all images (T2, FLAIR, T1, and T1 with contrast) two to three days following surgery. The surgical sealant continued to be visible, although degrading, through the 3 month scan and was no longer discernible in the 4, 5, and 6 month scans (T2 images). Histopathologic evaluations indicate that there were no morphologic changes associated with a single topical administration of Adherus AutoSpray Dural Sealant to a durotomy site in beagle dogs at seven days or at six months post-surgery.
Watertight Closure of Duraplasty Graphs in a Canine Durotomy Model	7 Canine 16 Weeks	Study performed to evaluate the in vivo compatibility of two commercially available xenograft duraplasty grafts (DuraGen® Dural Graft Matrix and Durepair® Dura Regeneration Matrix) with the use of Adherus AutoSpray Dural Sealant to augment dural closure and to evaluate the ability of Adherus AutoSpray Dural Sealant to create intraoperative watertight closures with these xenograft duraplasty grafts. Secondarily, the prevalence of postoperative CSF leakage and peridural adhesion formation was evaluated. After a 1.5 cm diameter durectomy was made, duraplasty grafts were placed and evaluated for CSF leaks through pressure testing via a Valsalva maneuver to 20 cm H_2O for 5 seconds. The designated animals then received the Adherus AutoSpray Dural Sealant. Intraoperative CSF leakage was assessed through pressure testing via a Valsalva maneuver to 20 cm H_2O for five seconds. The application of Adherus AutoSpray Dural Sealant produced no adverse test article-related effects in clinical observations, body weight, food consumption, physical or neurological parameters, or healing of the dura during this study. Adherus AutoSpray Dural Sealant maintained a watertight seal both intra-operatively, when challenged by Valsalva maneuver, and post-operatively, when imaged by MRI on Day 6 or 7. Animals that received treatment with Adherus AutoSpray Dural Sealant had significantly fewer adhesions between the bone flap and dura observed at necropsy and were able to maintain hyperphysiologic intracranial pressure induced with a saline infusion up to 75 to 80 cm H_2O. There were no morphologic changes related to the application of Adherus AutoSpray Dural Sealant observed during the MRI evaluations or at necropsy.

Test Performed	# of Animals Duration of Study	Summary/Relevant Findings
Tissue Sealants in a Canine Lumbar Durotomy Repair Model	20 Canine ●12 Test ●6 Control ●2 Comparative Control 4 Months	The objective of this GLP study was to evaluate the safety and effectiveness of Adherus AutoSpray Dural Sealant when used to provide watertight dural closure in a canine lumbar durotomy repair model. An additional objective of this study was to determine whether Adherus AutoSpray Dural Sealant would inhibit the formation of peridural fibrosis and dural adhesions as normal healing occurred. During surgery, the animals had two laminectomies performed, one at L2 and the other at L5, the exposed dura and arachnoid were incised to a length of 1 cm, the dural incision was closed with 6-0 nylon suture and Adherus AutoSpray Dural Sealant was applied in the treated animals (no test article was applied to the control animals). A hemilaminectomy was also made in the L3/L4 vertebra for pressure testing. Saline was infused to produce hyperphysiologic conditions to a maximum pressure of at least 40 cm of H_2O and was maintained for approximately 30 seconds to challenge the sealant The application of Adherus AutoSpray Dural Sealant produced no adverse test article-related effects in clinical observations, body weight, food consumption, physical or neurological parameters, clinical pathology parameters or CSF total cell count or chemistry parameters during this study. The Adherus AutoSpray Dural Sealant formulation was effective in obtaining an intra-operative watertight seal at average pressures up to 60 cm H_2O. This sealing efficacy carried over to the postoperative period in which the sealant treated animals continued to experience no CSF leaks, as determined by MRI evaluation. There was no histopathological evidence that application of Adherus AutoSpray Dural Sealant had any adverse effects on the adjacent tissues, including the spinal cord and spinal nerve roots. In addition, the application of Adherus AutoSpray Dural Sealant did not appear to impede healing of the surgical site. Adherus AutoSpray Dural Sealant, limited dural adhesions at both two months and four months. Peridural fibrosis and dura thickening/fibrosis were also reduced in animals that received the hydrogel formulation when compared to control animals which did not receive Adherus AutoSpray Dural Sealant.
Pharmacokinetics, Mass Balance and Tissue Distribution of Radioactivity	Sprague-Dawley Rats <u>Phase I</u> ●13 Rats 168 Hours Post Dose <u>Phase II</u> ●8 Active (Cranial) ●3 Control 504 Hours Post Dose	The objective of this study was to evaluate the pharmacokinetics, mass balance, and tissue distribution of radioactivity in rats following a single dural administration of [^{14}C]Erioglaucine (FD&C Blue #1) and [^{14}C]Tartrazine (FD&C Yellow #5) within Adherus AutoSpray Dural Sealant applied as a hydrogel disc to surgically created cranial defects. The study demonstrated that once Adherus AutoSpray Dural Sealant is applied to the dura, the dyes quickly extract from the gel (approximately within 1 week) and enter the bloodstream where they immediately distribute to the central compartment and are eliminated via the urine and feces. The mass balance recovery results demonstrated that renal elimination was the primary route of elimination, followed closely by fecal excretion. The results of this study demonstrate that the Adherus AutoSpray Dural Sealant dyes reside in the body for an insignificant period of time (less than 21 days).

C. <u>Additional Studies</u>

<u>Packaging:</u>

Testing was conducted to demonstrate that the packaging process and the product packaging met all package performance qualifications. Environmental conditioning testing was performed to assure that the product is not affected by stresses of shipping and handling.

Sterilization Testing:

E-beam sterilization validation was conducted for the Adherus® AutoSpray Dural Sealant to 25 kGy in order to achieve a Sterility Assurance Level of 10^{-6}. The study was based on Method VD_{max} of AAMI TIR 33:2005 (TIR 33) and ANSI/AAMI/ISO11137-2:2006.

Pyrogen Testing:

Bacterial endotoxin evaluation was conducted on three production lots/batches of the Adherus AutoSpray Dural Sealant. The specification for this design input is less than or equal to 2.15 EU/device (FDA recognized standard of 0.06 EU/mL for device contacting cerebrospinal fluid). Testing was accomplished utilizing the Kinematic Turbidimetric method. The results confirmed that each of the three lots had less than 0.050 EU/mL (less than 2.00 EU/device).

Shelf-Life:

A 12 month shelf life has been established based on the period of time that the device performance characteristics of set time, swelling, and burst strength retained their functionality, and package integrity was sufficient.

X. SUMMARY OF CLINICAL STUDIES

The applicant performed both feasibility and pivotal clinical studies to establish a reasonable assurance of safety and effectiveness of using the Adherus® AutoSpray Dural Sealant as an adjunct to standard methods of dural repair, such as sutures, to provide watertight closure during cranial procedures in the U.S. under IDE (Investigational Device Exemption) #G080198. Data from this clinical study were the basis for the PMA approval decision. A summary of the pivotal clinical study is presented below. Table 7 summarizes the study design and key results from the feasibility study.

Table 7: Summary of Adherus® AutoSpray Dural Sealant Feasibility Study

Study Design	# of Subjects	# of Sites	Primary Composite Endpoint	Secondary Safety Endpoints	Results
Prospective, non-controlled, multi-center, clinical feasibility study to evaluate the preliminary safety and effectiveness of the Adherus AutoSpray Dural Sealant in subjects scheduled for a cranial procedure involve a dural	25	4	Freedom from intra-operative CSF leakage from dural repair after up to 2 Adherus Dural Sealant applications, CSF leak/pseudomeningocele, and unplanned retreatment of the original surgical site within 120	Surgical site infection, meningitis, worsening Modified Rankin Score, surgical site swelling, and adverse events through the 120 day follow-up period.	The primary composite endpoint evaluation demonstrated 90.9% device success at 120 days post-procedure. None of the treated subjects experienced intra-operative CSF leaks during the first post-sealant Valsalva maneuver (up to 20 cm H_2O for 5-10 seconds), and no subjects required a second application of the sealant. Two subjects

incision. The subjects were followed for 48 hours post index-procedure, and then at 14, 45, 120 and 180 days post-index procedure.			days post-surgery.		experienced a CSF leak or pseudomeningocele post-surgery, and one of these subjects had unplanned retreatment of the original surgical site for CSF leak. The results of the secondary safety endpoint analyses showed that there were no unanticipated adverse device effects. There were a total of 22 serious adverse events reported among 10 subjects, and 24 subjects experienced at least one adverse event within the 120 day follow-up period. The type and rate of adverse events observed in the study were consistent with the complexity of the surgical procedure and the co-morbid condition of the treated subjects.

A. Pivotal Study Design

Subjects were treated between September 3, 2010 and September 28, 2013. The database for this PMA reflected data collected through January 17, 2013 and included 250 patients. There were 27 investigational sites.

The study was a prospective, randomized, controlled, multi-center pivotal clinical study. Subjects were assigned an intervention in a 1:1 randomization allocation ratio, stratified by clinical center and surgical procedure: supratentorial (ST) and infratentorial (IT) approach. Subjects were evaluated between postoperative days 1-4 or hospital discharge, whichever occurred first, and at 14, 45, and 120 days post-index procedure. The primary analysis was a responder analysis using a one-sided normal approximated z-test for proportion test to test the null hypothesis of the proportion of subjects meeting individual successful composite endpoint in the Adherus® arm being inferior to the control arm by at least 10%. Adjustment for multiplicity following Hochberg's approach was planned for the secondary endpoints intended to support labeling claims. The trial was partially single-blinded. It was not possible to blind surgeons to the device used. Subjects and core laboratory evaluators were masked to the study treatment assignments.

The clinical study for the Adherus® AutoSpray Dural Sealant utilized a Core Neuroradiology Laboratory, Medical Monitor, and Clinical Events Committee to adjudicate and oversee the clinical data obtained from the study.

The control device was the commercially available DuraSeal Dural Sealant System (P040034). The trial was designed to demonstrate non-inferiority of the Adherus® AutoSpray Dural Sealant System to the DuraSeal Dural Sealant System when used in conjunction with standard methods of dural repair in cranial procedures.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the pivotal study was limited to subjects who met the following criteria:

   Pre-Operative Inclusion Criteria:
   - Subject was ≥ 18 and ≤ 75 years of age.
   - Subject was scheduled for an elective cranial procedure involving a dural incision using any of the following surgical locations/approaches (or combination): frontal, temporal, occipital and parietal (i.e., supratentorial), and/or midline or lateral suboccipital (i.e., infratentorial).
   - Subject required a procedure involving a Class I/clean wound (uninfected surgical wound in which no inflammation was encountered).
   - Subject was able and willing to provide informed consent and HIPAA authorization.
   - Subject was able and willing to meet all study requirements, including attending all post-index procedure assessment visits and radiological tests.

   Intra-Operative Inclusion Criteria:
   - Subject's linear extent of durotomy was ≥ 2 cm.
   - Subject's dural margins from the edges of bony defect were ≥ 3 mm throughout.
   - Subject's CSF leak was present intra-operatively following completion of primary dural closure (with or without non-autologous duraplasty or autologous tissue), either spontaneously or upon Valsalva maneuver, at up to 20 cm H_2O for up to five (5) seconds.

   Pre-Operative Exclusion Criteria:
   - Subject required a procedure involving a translabyrinthine, transsphenoidal, transoral approach, or any procedure that penetrates the air sinus or mastoid air cells. Note: Superficial penetration of mastoid air cells was not an exclusion if cells were appropriately sealed (e.g., bone wax).
   - Subject had a CSF shunt such as; ventriculo-peritoneal, ventriculo-pleural, ventriculo-atrial or lumbo-peritoneal shunts.
   - Subject had an external ventricular or lumbar CSF drain that must be left in place after surgery.
   - Subject had clinically significant hydrocephalus or clinical evidence of altered CSF dynamics.
   - Subject had undergone a previous intracranial neurosurgical procedure in the same anatomical location. (Note: stereotactic biopsy was not exclusionary).
   - Subject experienced previous CSF leak (secondary to trauma, neoplasm, surgery or other etiology).

- Subject had radiation treatment to the surgical site, or standard fractionated radiation therapy was planned within ten days post index-procedure. (Note: stereotactic radiosurgery prior to the planned index procedure was not an exclusion criterion.)
- Subject had experienced a traumatic injury to the head within 30 days prior to the planned index procedure resulting in basilar skull fracture or fractures involving the paranasal sinuses.
- Subject had metallic implant(s) that are not MRI compatible, e.g., cochlear implant, neurostimulator, stent, surgical clip, cardiac pacemakers, or other non-MRI compatible implants, or an elective implant of such devices was planned during the course of the study. Note: mercury amalgam dental fillings or similar metallic dental prostheses were not an exclusion criterion.
- Subject had a known malignancy or another condition with anticipated survival shorter than six months.
- Subject had undergone chemotherapy treatment, excluding hormonal therapy, within three weeks prior to the planned index procedure, or use of intracavitary chemotherapy wafer (BCNU) was planned, or chemotherapy treatment was planned within two weeks after the index procedure was performed.
- Standard use of peri-operative steroids (i.e., corticosteroids) was permitted. Chronic steroid use (defined as daily use of corticosteroids for $\geq$ 8 weeks) for the purposes of reducing the side effects of chemotherapy and/or radiation therapy for cancer was not exclusionary unless the patient was deemed by the investigator to be suffering from steroid toxicity (i.e., Cushing's syndrome) manifested by symptoms and signs such as thin skin, striae, easy bruising, muscle atrophy, upper body obesity, severe fatigue, etc. Use of corticosteroids on a chronic basis (as defined previously) for purposes other than decreasing the symptoms of systemic chemotherapy was exclusionary unless those steroids were discontinued 4 weeks prior to the planned index procedure.
- Subject received warfarin, heparin, other anticoagulant agents, aspirin or non-steroid anti-inflammatory agents on a daily basis and pre-surgical, standard of care drug wash-out did not occur.
- Subject had a documented clinically significant coagulopathy with a partial thromboplastin time (PTT) > 37 seconds, or international normalized ratio (INR) > 1.3 INR units.
- Subject had a compromised immune system or autoimmune disease, or was on chronic immunosuppressant agents at baseline.
- Subject had a systemic infection or evidence of any infection near planned operative site.
- Subject had a serum creatinine level > 2.0 mg/dL.
- Subject had a serum total bilirubin > 2.5 mg/dL at baseline.
- Subject had uncontrolled diabetes as evidenced by the Institution’s standard of care (HbA1c > 7%, blood glucose, etc.) at baseline.
- Subject had a known allergy to FD&C Blue #1 and/or FD&C Yellow #5.
- Subject was pregnant, breast-feeding, or intended to become pregnant during the course of the study.

- Subject was participating in a clinical trial of another investigational drug or device and had not completed the required follow-up period.
- Subject had been previously enrolled in an Adherus Dural Sealant System study.

Intra-Operative Exclusion Criteria:

- Subject had an incidental finding that met any pre-operative exclusion criterion listed above.
- Subject required the intra-operative placement of a CSF diversion device (e.g., ventricular catheter, subdural catheter, lumbar drain, or other device designed to externally evacuate CSF) that was left in place after the procedure. Note: Subgaleal drains used for acute post-operative management of the incision site were permitted.
- Subject had a gap > 2 mm present between dural edges, or between the edge of dura and duraplasty material, based on visual estimate by surgeon before application of the surgical sealant.

2. Follow-up Schedule

All subjects were scheduled to return for follow-up examinations at post-operative days 1-4, or hospital discharge, whichever occurred first, and at 14, 45, and 120 days post-index procedure.

Preoperatively, the subjects were evaluated with a modified physical exam, neurological exam, pregnancy test, serum chemistry/complete blood count (CBC)/PTT/INR, and magnetic resonance MRI/computed tomography (CT) imaging. Postoperatively, the objective parameters measuring during the study included the modified physical exam (all visits), neurological exam (all visits), Modified Rankin Scale (only day 14, 45, and 120 day visits), serum chemistry/CBC/PTT/INR (only 120 day visit), MRI/CT (only 120 day visit), and CSF leak and pseudomeningocele assessment (all visits). Consented subjects who did not meet all eligibility criteria were considered screen failures and were not randomized to receive the Adherus AutoSpray Dural Sealant or the control device. The procedures and assessments at every visit are shown below in Table 8. Adverse events and complications were recorded at all visits.

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

Table 8: Schedule of Study Procedures

Activity	Visit 1 Baseline (Pre-op visit) Within 30 days prior to planned craniotomy[5]	Visit 2 Craniotomy (Surgery Day)	Visit 3 Post-Surgery Evaluation (between 1-4 days post-surgery or hospital discharge, whichever occurs first)	Visit 4 14 days post-surgery (+/- 7 days)	Visit 5 45 days post-surgery (+/- 14 Days)	Visit 6 120 days post surgery (+/- 14 days)
Signed Informed Consent obtained	X					
Demographics, Medical / Surgical History obtained	X					
Modified physical exam	X		X	X	X	X
Pre-op Inclusion / exclusion criteria determination	X					
Neurological exam	X		X	X	X	X
Modified Rankin Scale	X			X	X	X
Pregnancy test[1]	X					
Serum chemistry / CBC / PTT / INR[2]	X					X
MRI/CT[3, 4, 5]	X					X[4]
Intraoperative eligibility criteria determination		X				
Randomization		X				
Craniotomy with randomized treatment		X				
CSF Leak and Pseudomeningocele assessment		X[3]	X[3]	X[3]	X[3]	X[3]
Adverse Event Assessment[3]	X	X	X[3]	X[3]	X[3]	X[3]

1. Only for females of childbearing potential. Obtained within 3 days prior to planned craniotomy.
2. PTT and INR at baseline only
3. An MRI was required at any post-operative visit if a CSF leak or pseudomeningocele was suspected. If the results from a CT indicated a suspected leak, an MRI must also be obtained; see Section 12.7.
4. The imaging technique used at baseline was preferred to be the same technique used for the 120-day image.
5. The Baseline MRI/CT image does not need to be completed within 30 days of procedure.

3. Clinical Endpoints

With regards to safety and effectiveness, the primary endpoint was based on individual treatment success rates during the 120-day post-index procedure follow-up period; it was a composite binary endpoint, with individual subjects considered successes if free of all 3 of the following:

- Intra-operative CSF leakage from dural repair after up to two Adherus/control applications during Valsalva maneuver up to 20cm H_2O for up to 5 seconds.
- CSF leak or pseudomeningocele diagnosed by physical examination, biochemical assay or imaging study.
- Unplanned retreatment of the original surgical site adjudicated by the Clinical Events Committee (CEC) to be device-related, including meningitis or the management of deep infection, minimally invasive procedures or return to the operating room for neurosurgical complications other than CSF leak or

pseudomeningocele formation or those related to the subject's pre-existing condition.

The secondary endpoints in the clinical study were intended to support labeling claims, which are only made after the primary endpoint of the study was met.

Secondary endpoints intended for labeling claims included:

- CSF leak or pseudomeningocele diagnosed by physical examination, biochemical assay or imaging study during the 120-day follow-up period following the index procedure.
- Unplanned retreatment of the original surgical site adjudicated by the CEC to be device-related, including meningitis or the management of deep infection, minimally invasive procedures or return to the operating room for neurosurgical complications other than CSF leak or pseudomeningocele formation or those related to the subject's pre-existing condition, during the 120-day follow-up period following original surgical procedure.

Secondary endpoints not intended for labeling claims included:

- Intra-operative CSF leakage from dural repair after up to two Adherus/control applications during Valsalva maneuver up to 20cm H_2O for up to 5 seconds
- Surgical wound infections or meningitis during the 120-day follow-up period.
- Device-related adverse events: device-related adverse events included all adverse events classified as definitely, probably, possibly or undetermined relation to the device or procedure.
- Postoperative neurological function decline at the 120-day follow-up study assessment.
- Wound healing at the 120-day follow-up assessment.
- Time-to-event of the following events:
  - Treatment failure defined as failure to meet the primary composite evaluation
  - Postoperative CSF leak or pseudomeningocele diagnosed by physical examination, biochemical assay or imaging. Unplanned retreatment of the original surgical site adjudicated by the CEC to be device-related, including meningitis or the management of deep infection, minimally invasive procedures or return to the operating room for neurosurgical complications other than CSF leak or pseudomeningocele formation or those related to the subject's pre-existing condition, during the 120-day follow-up period following original surgical procedure
  - Death (from any cause)

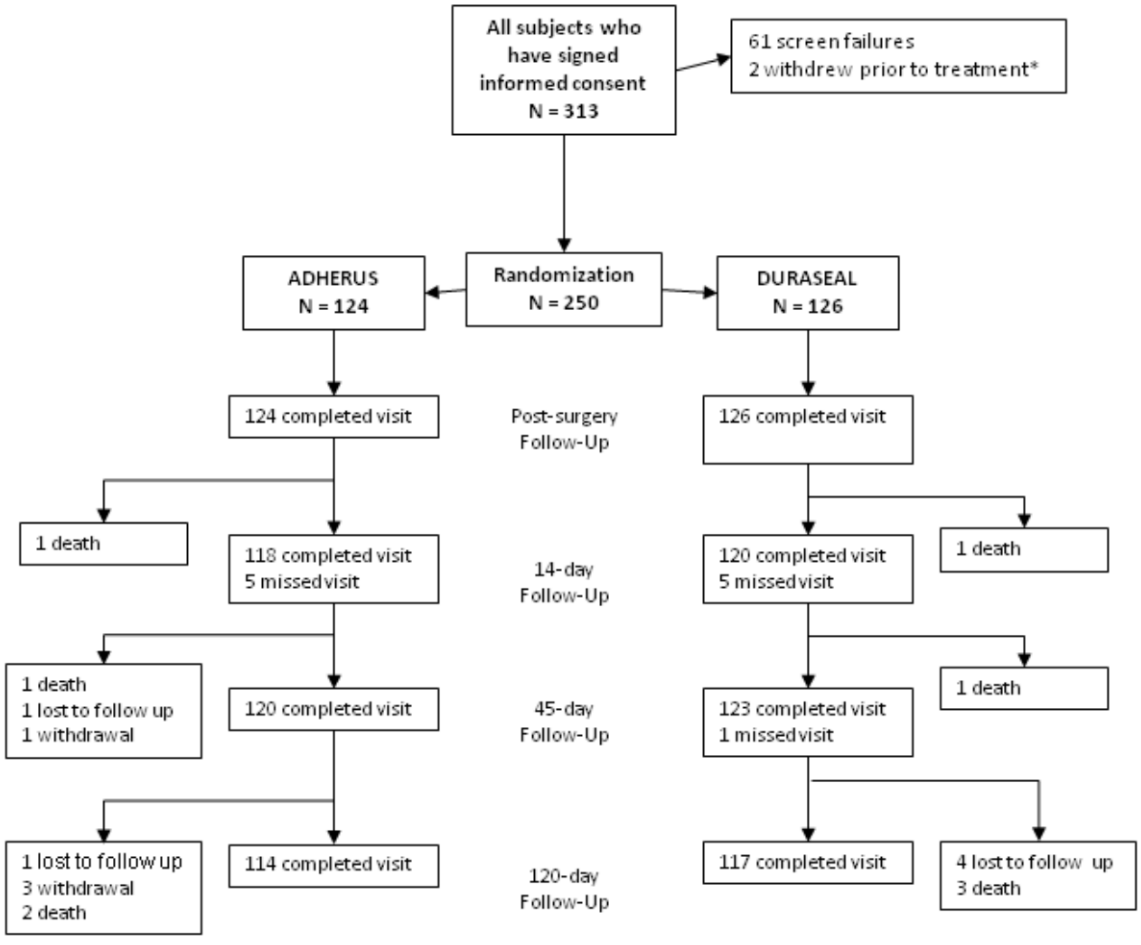
With regard to success/failure criteria, the study was considered a success if the proportion of subjects achieving an individual successful outcome (responder) that received treatment with Adherus® was statistically significantly non-inferior to the proportion of subjects achieving individual success when treated with the control (DuraSeal Dural Sealant System). Statistical significance was defined as a p-value resulting from the primary composite endpoint analysis using a one-sided

normal approximated z-test for proportion that was ≤ 0.05. After the claim of study success is made, a superiority test is performed for a superiority claim by using the same approach. Secondary endpoints intended to support labeling claims were analyzed by using a one-sided Fisher's exact test for superiority. Adjustment for multiplicity following Hochberg's approach was planned for the secondary endpoints intended to support labeling claims.

B. Accountability of PMA Cohort

At the time of database lock, of 250 subjects enrolled in the PMA study, 231 (92.4%) subjects were available for analysis at the completion of the study, the 120-day post-operative visit. Figure 2 details the number of subjects who completed each visit. In addition, Table 9 shows the number of subjects sorted by the analysis populations (i.e., per-protocol (PP), intent-to-treat (ITT), modified intent-to-treat (MITT)).

Figure 2: Intent-to-Treat Subject Disposition



* One subject at site 04 signed informed consent; however was withdrawn prior to treatment due to a serious adverse event. Site 11 consented one subject after notification of impending site closure.

Table 9: Number of Subjects by Analysis Population

Study Population	Adherus	Control	Total
ITT (Device Assigned)	124	126	250
MITT (Device Completed)	120	122	242
Per-Protocol (Device Completed)	114	117	231
Completers (Device Completed)	114	117	231

A total of nineteen randomized subjects (10 Adherus, 9 control) withdrew by the 120-day visit. Six subjects (2 Adherus subjects, 4 control) were lost to follow-up and nine subjects (4 Adherus subjects, 5 control) died prior to completing the 120-day visit. In addition, four Adherus subjects withdrew prior to reaching the 120-day visit. Of the four Adherus withdrawals, one subject was placed in hospice, and the family requested withdrawal. Another Adherus subject withdrew due to being incarcerated before the 120-day visit. Withdrawal was requested by the physician for a third Adherus subject as the subject was diagnosed with a glioblastoma multiforme and elected to enroll into a different clinical trial for treatment. The fourth early withdrawal subject was randomized to receive Adherus, but did not receive Adherus or control due to an operator error during device assembly during the procedure.

A total of 266 protocol deviations in 149 subjects (120 deviations in 71 Adherus subjects, 146 deviations in 78 control subjects) were reported. They included:

- Twenty-three deviations of enrolling subjects who should be excluded (9 deviations in 8 Adherus subjects and 14 deviations in 12 control subjects)
- Sixteen "other" protocol deviations (10 deviations in 10 Adherus subjects, 6 deviations in 5 control subjects) included SAE notifications reported out of window, an incorrect randomization envelope was opened, or a subject was not treated in accordance with randomization assignment due to a device assembly error during the procedure.
- Ninety-three "failure to perform a requisite study procedure" deviations (44 deviations in 32 Adherus subjects and 49 deviations in 32 control subjects)
- The remaining protocol deviations included issues related to inadequate informed consent or re-consent process, late or missed follow-up visits as well as study procedure done outside of time windows.

Large number of protocol violations may reflect the difficulty of conducting this type of study and implementing its data monitoring procedures. However, the incidence and nature of protocol deviations appear to be similar among Adherus subjects and control subjects.

C. PMA Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal clinical study performed in the US (see Table 10).

Table 10: Subject Baseline Demographics and Treatment Parameters (ITT)

Characteristics	Adherus AutoSpray Dural Sealant Population	Control Population
Number of Subjects	124	126
Men/Women	41/83	40/86
Median Age (years)	54.2	51.1
Subject ASA score (N (%))		
I	2 (1.6)	8 (6.3)
II	47 (37.9)	50 (39.7)
III	69 (55.6)	62 (49.2)
IV	6 (4.8)	6 (4.8)
V	0 (0.0)	0 (0.0)
Primary indication for surgery (N (%))		
Tumor	56 (45.2)	53 (42.1)
Epilepsy	1 (0.8)	1 (0.8)
Nerve decompression	17 (13.7)	21 (16.7)
AVM	3 (2.4)	5 (4.0)
Aneurysm	28 (22.6)	26 (21.3)
Chiari malformation	17 (13.7)	18 (14.3)
Cyst	2 (1.6)	1 (0.8)
Other	0 (0.0)	1 (0.8)
Approach (N (%))		
Infratentorial	53 (42.7)	52 (41.3)
Supratentorial	71 (57.3)	74 (58.7)
Primary technique for dural closure (N (%))		
Suture	48 (38.7)	48 (38.1)
Suture + autologous dural material	29 (23.4)	34 (27.0)
Suture + non-autologous dural material	45 (36.3)	39 31.0)

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the per-protocol (PP) cohort of 231 patients available for the 120-day post-surgery evaluation. The key safety outcomes for this study are described below. Adverse effects occurring at a rate of ≥ 1% for Adherus® AutoSpray Dural Sealant treated patients are reported in Table 1 in Section VIII of this document.

Adverse effects that occurred in the PMA clinical study:

Safety was assessed based on evaluation of wound healing, surgical site infections, meningitis, worsening Modified Rankin Score, surgical site swelling, and adverse events through the 120 day follow-up period. One hundred (80.6%) subjects in the Adherus® AutoSpray Dural Sealant group and 98 (77.8%) subjects in the control group experienced at least one adverse event (AE) within the 120 day follow-up period. This result is expected given the disease-state of the group under study (71 Adherus® AutoSpray Dural Sealant subjects, 64 control subjects had ASA score ≥ III at baseline). The majority of AEs were mild or moderate in severity, and over half of the AEs in each treatment group had resolved by the date of study completion. There were no unanticipated adverse device effects (UADE).

The most commonly reported adverse events were: headache (11.3% Adherus subjects, 12.7% control subjects); pseudomeningocele (7.3% Adherus subjects, 4.8% control subjects); hypoaesthesia (3.2% Adherus subjects, 7.1% control subjects); vision blurred (5.6% Adherus subjects, 5.6% control subjects); dizziness (5.6% Adherus subjects, 3.2% control subjects); and convulsion (4.0% Adherus subjects, 2.4% control subjects). The spectrum of symptoms can be part of the natural history of the conditions which were treated.

The incidence of serious adverse events (SAEs) was comparable between the two groups. There were 41 SAEs among 33 (26.6%) Adherus® AutoSpray Dural Sealant subjects and 40 SAEs among 33 (26.2%) control subjects. Seven (5.6%) Adherus® AutoSpray Dural Sealant subjects had 8 serious AEs adjudicated by the CEC as device-related coded as pseudomeningocele (n=3), convulsion (n=1), dysphagia (n=1), headache (n=1), extradural haematoma (n=1), and respiratory failure (n=1). Five (4.0%) control subjects had five serious device-related AEs coded as incision site infection (n=2), intracranial venous sinus thrombosis (n=1), infection (n=1), and pseudomeningocele (n=1).

Among the subjects treated with Adherus® AutoSpray Dural Sealant, there were no device related deep wound infections and no cases of meningitis. Subjects in the control group experienced two device related deep wound infections and no cases of meningitis.

Nine deaths occurred over the course of the 120-day study (4 Adherus® AutoSpray Dural Sealant subjects, 5 control subjects). All deaths were adjudicated as not related to the device. One death in the Adherus® AutoSpray Dural Sealant group was determined to be definitely procedure-related, and one death in the control group was possibly procedure-related. The remaining seven deaths were not related to the procedure. Deaths among the Adherus® AutoSpray Dural Sealant subjects were attributed to complications from colitis, stroke, disease progression, and metastatic lung cancer. Deaths among the control subjects were attributed to disease progression, multi-organ failure and pneumonia, respiratory failure, and posterior herniation with severe brain injury.

The type and rate of adverse events observed in this study are consistent with the complexity of the surgical procedure and the co-morbid condition of the treated subjects.

2. Effectiveness Results

The analysis of effectiveness was based on all subjects who received treatment (per-protocol (PP) population) evaluable at the 120-day time point. Key effectiveness outcomes are presented in Table 11. The overall success rate for PP analysis was 91.2% in the Adherus® AutoSpray Dural Sealant group compared to 90.6% in the control group.

Statistical Model:

The statistical model used is a responder analysis of the difference in success proportions of individual composite success between the two treatment groups. The two success rates were compared by using a one-sided normal approximated z-test for two independent proportions with a pre-defined non-inferiority margin of 10%.

Hypothesis:

P_A and P_C represent the proportion of subjects who are considered composite successes in the Adherus and DuraSeal control arms, and with a non-inferiority margin $\delta = 0.10$, the hypotheses are:

$$H_0 : P_A \leq P_C - 0.1 \qquad \text{vs.} \qquad H_A : P_A > P_C - 0.1$$

Non-inferiority of Adherus® to the control will be concluded if the null hypothesis is rejected. If non-inferiority is supported, a subsequent superiority test would be conducted.

Within the PP analysis group, Adherus® AutoSpray Dural Sealant was found to be statistically significantly non-inferior to the control with respect to the overall success rate at 120 days with a non-inferiority margin of 10% (p=0.005). All

(100%) Adherus® AutoSpray Dural Sealant subjects were free of intra-operative CSF leakage from dural repair after up to two dural sealant applications during Valsalva maneuver up to 20 cm H_2O for up to 5 seconds compared with 116/117 (99.1%) control subjects. 105/114 (92.1%) Adherus® AutoSpray Dural Sealant subjects and 109/117 (93.2%) control subjects were free of a CSF leak or possible pseudomeningocele during the 120-day follow-up period. Also, 113/114 (99.1%) Adherus® AutoSpray Dural Sealant subjects and 115/117 (98.3%) control subjects were free of unplanned retreatment of the original surgical site adjudicated by the CEC as device-related.

The success rate of the Adherus group was nominally higher than the control group at the 14-day and 45-day follow-ups in the PP population (Fisher's exact test $p < 0.001$). Therefore, the results are consistent with the study's conclusion that Adherus treatment is non-inferior to the control treatment.

For the primary endpoint, Adherus was found to be non-inferior to the control with the non-inferiority margin of 10% in the PP population ($p = 0.005$). The results of the MITT and ITT analysis populations ($p = 0.015$ and $p = 0.020$, respectively) were consistent with and supportive of the primary analysis results from the PP analysis population.

There were a number of protocol deviations in the protocol. A sensitivity analysis was performed to examine whether the outcome and interpretation of the study was affected by excluding the mistakenly-enrolled subjects. The study's main conclusions, namely Adherus is non-inferior to the control in the composite success endpoint, stays the same; the analyses' p-values for the PP, MITT, and ITT populations were 0.005, 0.014, and 0.018, respectively.

Both pre-specified secondary endpoints were intended to be tested for superiority to support labeling claims. However superiority was not met in either case and labeling claims will not be sought.

Table 11: Summary of Primary Composite Endpoint during 120 Days Follow-Up – PP Population

Primary Endpoint Component	Adherus	Control
Subjects free of intra-operative CSF leakage after up to two dural sealant applications		
n/N (%)	114/114 (100.0)	116/117 (99.1)
95% CI	(96.8, 100.0)	(95.3, 100.0)
Primary Endpoint Component	**Adherus**	**Control**
Subjects free of CSF leak or pseudomeningocele diagnosed by physical examination/ biochemical assay/ imaging study within 120 days		
n/N (%)	105/114 (92.1)	109/117 (93.2)
95% CI	(85.5, 96.3)	(87.0, 97.0)
Subjects free of unplanned treatment of the original surgical site adjudicated by the CEC to be device-related		
n/N (%)	113/114 (99.1)	115/117 (98.3)
95% CI	(95.2, 100.0)	(94.0, 99.8)
Overall success		
n/N (%)	104/114 (91.2)	106/117 (90.6)
95% CI	(84.5, 95.7)	(83.8, 95.2)
P-value (difference between groups; delta = 10%)	0.0049	
P-value (superior)	0.4339	

A secondary analysis used stepwise logistic regression to examine if the observed treatment effect was mediated by any baseline covariates of interest, including: treatment group, gender, age, indication for craniotomy (chiari malformation, tumor, nerve decompression, and aneurysm), use of non-autologous materials, use of autologous materials, ASA score, surgical approach, volume to length ratio, number of dural sealant applications, incision type, treatment-age interaction term, treatment-chiari malformation interaction term, and treatment-non-autologous material interaction term. None of the main effects or treatment-by-covariate interactions except the use of non-autologous duraplasty materials was statistically significant.

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: gender and race. Gender and race effects were not found to be significant in affecting the primary composite endpoints.

Tables 12 and 13 present the primary composite endpoint results by gender and race, respectively for the PP analysis population.

Table 12: Summary of Primary Composite Endpoint by Gender for PP Population

	Female		Male	
Primary Endpoint Component	Adherus	Control	Adherus	Control
Subjects free of intra-operative CSF leakage after up to two dural sealant applications				
n/N (%)	74/74 (100.0)	80/81 (98.8)	40/40 (100.0)	36/36 (100.0)
95% CI	(95.1, 100.0)	(93.3, 100.0)	(91.2, 100.0)	(90.3, 100.0)
Subjects free of CSF leak or pseudomeningocele diagnosed by physical examination/ biochemical assay/ imaging study within 120 days				
n/N (%)	67/74 (90.5)	78/81 (96.3)	38/40 (95.0)	31/36 (86.1)
95% CI	(81.5, 96.1)	(89.6, 99.2)	(83.1, 99.4)	(70.5, 95.3)
Subjects free of unplanned treatment of the original surgical site adjudicated by the CEC to be device-related				
n/N (%)	73/74 (98.6)	81/81 (100.0)	40/40 (100.0)	34/36 (94.4)
95% CI	(92.7, 100.0)	(95.5, 100.0)	(91.2, 100.0)	(81.3, 99.3)
Overall success**				
n/N (%)	66/74 (89.2)	77/81 (95.1)	38/40 (95.0)	29/36 (80.6)
95% CI	(79.8, 95.2)	(87.8, 98.6)	(83.1, 99.4)	(64.0, 91.8)

** P-value of 0.024 on the Treatment * Gender interaction term in Logistic Regression model that also included gender and treatment effects (both non-significant).

Table 13: Summary of Primary Composite Endpoint by Race for PP Population

	Non-White		White	
Primary Endpoint Component	Adherus	Control	Adherus	Control
Subjects free of intra-operative CSF leakage after up to two dural sealant applications				
n/N (%)	9/9 (100.0)	10/10 (100.0)	105/105 (100.0)	106/107 (99.1)
95% CI	(66.4, 100.0)	(69.2, 100.0)	(96.5, 100.0)	(94.9, 100.0)
Subjects free of CSF leak or pseudomeningocele diagnosed by physical examination/ biochemical assay/ imaging study within 120 days				
n/N (%)	7/9 (77.8)	8/10 (80.0)	98/105 (93.3)	101/107 (94.4)
95% CI	(40.0, 97.2)	(44.4, 97.5)	(86.7, 97.3)	(88.2, 97.9)
Subjects free of unplanned treatment of the original surgical site adjudicated by the CEC to be device-related				
n/N (%)	9/9 (100.0)	10/10 (100.0)	104/105 (99.0)	105/107 (98.1)
95% CI	(66.4, 100.0)	(69.2, 100.0)	(94.8, 100.0)	(93.4, 99.8)
Overall success**				
n/N (%)	7/9 (77.8)	8/10 (80.0)	97/105 (92.4)	98/107 (91.6)
95% CI	(40.0, 97.2)	(44.4, 97.5)	(85.5, 96.7)	(84.6, 96.1)

** P-value of 0.8452 on the Treatment * Race interaction term in Logistic Regression model that also included race and treatment effects. Race was not significant (p=0.069).

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 27 investigators of which none were full-time or part-time employees of the sponsor and 1 of the investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1
- Significant payment of other sorts: 1
- Proprietary interest in the product tested held by the investigator: None
- Significant equity interest held by investigator in sponsor of covered study: None

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

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

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Neurological Devices Panel of the Medical Devices Advisory Committee, an FDA advisory committee, for review and recommendation, because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The Adherus® AutoSpray Dural Sealant met its pre-specified effectiveness endpoint in that the proportion of subjects who were classified as demonstrating success in the composite primary endpoint at the 120-day follow-up visit was statistically significantly non-inferior to the control DuraSeal.

B. Safety Conclusions

The type and rate of adverse events observed in this study are consistent with the complexity of the surgical procedure and the co-morbid condition of the treated subjects. The Adherus and control DuraSeal appear to have similar safety profile.

C. Benefit-Risk Conclusions

The data support that the benefits of using the Adherus® AutoSpray Dural Sealant outweigh the risks when the device is used as indicated and in accordance with the directions for use.

Furthermore, per Section 302 of the Medical Device User Fee Amendments of 2007, the FDA may leverage adult data to indicate a device for the pediatric population. The age range of the study population was 19-75 years for Adherus and 19-75 years for Control. Because post pubertal patients have a similar cerebral physiology to adult patients, the indicated population may include patients who are at least 13 years of age.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The results from the preclinical studies indicate that the Adherus® AutoSpray Dural

Sealant meets the safety and performance specifications set. Data collected from a multi-center clinical investigation of the performance of the Adherus® AutoSpray Dural Sealant provides assurance of product safety and effectiveness when the device is used in accordance with the labeling.

XIII. CDRH DECISION

CDRH issued an approval order on March 30, 2015.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

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