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A Prospective Randomized Controlled Study Evaluating the Safety and Efficacy of EVICEL® used for Suture-Line Sealing in Dura-Mater Closure during Paediatric Neurosurgical Cranial Procedures

The Paediatric EVICEL® Neuro Study

Protocol Number: BIOS-13-006

Document	Effective Date
Original Protocol	18 February 2014
Administrative Change 01	03 December 2014
Administrative Change 02	29 June 2015
Administrative Change 03	09 January 2017
Amendment 01	06 March 2018
Administrative Change 04	15 May 2020

Sponsor:

ETHICON Inc.
P.O. Box 151,
Route 22 West
Somerville, NJ 08876

Responsibilities for the conduct of this clinical study have been transferred from Ethicon Inc. to:

Ethicon, a division of J&J Medical Ltd.
Baird House
4 Lower Gilmore Bank
Edinburgh, EH3 9QP
United Kingdom

CONFIDENTIALITY STATEMENT

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[redacted]

COMPLIANCE STATEMENT

This study will be conducted in accordance with specific provisions of the associated IRB/IECs, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical practice (GCP) and the applicable national and regional regulatory requirement(s).

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Principal Investigator Agreement:

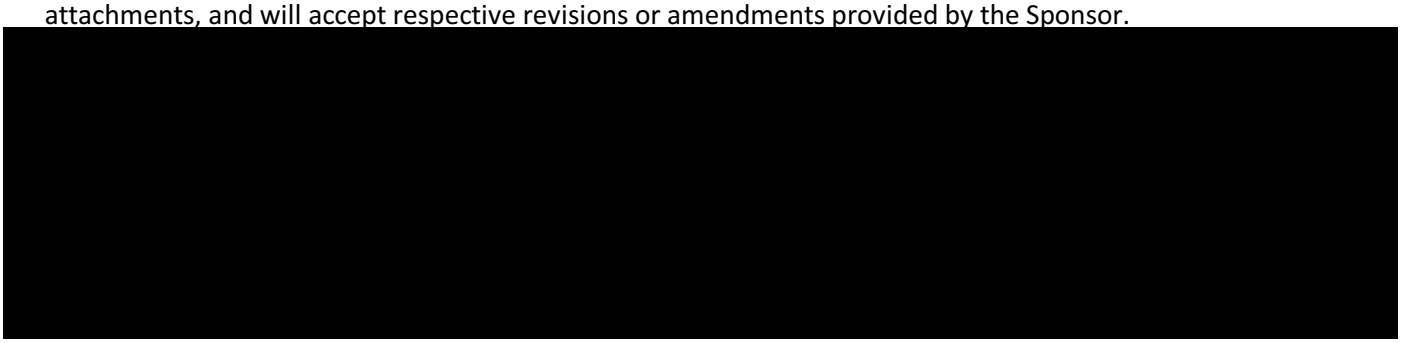
I have read this protocol and agree to conduct this clinical investigation in accordance with the design and specific provisions outlined herein. I understand the protocol, and I understand I am solely responsible to ensure the investigation is conducted in accordance with Good Clinical Practices (GCP), applicable country regulations the Declaration of Helsinki, the signed clinical study contract with Sponsor and with the protocol outlined herein. I will conduct this study as outlined therein and will make reasonable effort to complete the study within the time period designated by the Sponsor.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who will assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the product and the conduct of the study.

I will fulfill the requirements of my Institutional Review Board (IRB)/Ethics Committee (EC), or other oversight committee, to ensure complete and continual oversight of this clinical investigation. I will use an Informed Consent Document approved by the Sponsor and my reviewing IRB/EC (where required).

I agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events, product related adverse events, or procedure related adverse events as defined in this protocol to the Sponsor, and comply with all adverse event reporting requirements of my reviewing IRB/EC. I agree to permit the Sponsor, its authorized representatives, my reviewing IRB/EC, and any regulatory authority/body access to all records relating to the clinical investigation.

The below signature confirms I have read and understood this protocol and its associated amendments or attachments, and will accept respective revisions or amendments provided by the Sponsor.



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A Prospective Randomized Controlled Clinic Study Evaluating the Safety and Efficacy of EVICEL® used for Suture-Line Sealing in Dura-Mater Closure during Paediatric Neurosurgical Cranial Procedures

SYNOPSIS

OBJECTIVE: To evaluate the safety and efficacy of EVICEL® when used for suture-line sealing in dura-mater closure in elective or urgent paediatric cranial neurosurgery to provide intraoperative watertight closure.

STUDY DESIGN: This is a prospective randomized, open-label, multi-center controlled study evaluating the effectiveness of EVICEL® as an adjunct to sutured dural closure compared to control to obtain an intraoperative watertight dural closure.

Paediatric subjects, undergoing elective or urgent craniotomy/craniectomy for pathological processes in the posterior fossa (such as benign or malignant tumors, vascular malformations, and Chiari 1 malformations) or in the supratentorial region and who were demonstrated to have persistent cerebrospinal fluid (CSF) leakage following a primary attempt at suture closure of the dural incision.

Paediatric subjects for this study are classified as:

- Newborn infants (birth to 27 days. Pre-term newborn infants born ≤ 37 weeks gestation will be included within the group)
- Infants and toddlers (28 days to <24 months)
- Children (2 to 11 years)
- Adolescents (12 to <18 years)

42 paediatric subjects with intra-operative cerebrospinal fluid (CSF) leak following primary suturing of the dura will be randomized in a 2:1 allocation ratio and will be stratified by surgical procedure, posterior fossa or supratentorial to either EVICEL® Fibrin Sealant (Human) or additional dural sutures.

Subjects will be followed post-operatively through discharge and for 30 days (±3 days) post-surgery. The incidence of CSF leaks will be assessed within 5 days (± 2 days) and 30 days (±3 days) post-operatively as detected by any of the following: clinical observation, diagnostic testing or the need for surgical intervention to treat a CSF leak or pseudomeningocele.

SUBJECTS RANDOMIZED TO EVICEL®

For subjects randomized to receive EVICEL® Fibrin Sealant (Human), a thin layer will be applied to the entire length of the suture line and the adjacent area to at least 5mm away, including all suture holes. If necessary, a second layer of EVICEL® may be applied. A cure time 1-2 minutes should be allotted between layers to allow for polymerization. CSF leakage will be evaluated with a Valsalva maneuver 20-25 cm H_2O for 5-10 seconds.

If CSF leakage is still apparent a second treatment (up to two layers) with EVICEL® may be applied. CSF leakage will be re-evaluated with a second Valsalva maneuver 20-25 cm H_2O for 5-10 seconds.

- If watertight closure is not evident after this final Valsalva maneuver, the subject will be deemed a failure and the surgeon may revert to his/her standard of care for closure including the use of other commercially available fibrin sealants (except EVICEL®) or an onlay dural patch.

- If watertight closure is achieved, no further treatment, including the use of onlays, will be allowed.

Closure of the remaining layers of the surgical site will be performed according to the surgeon's standard of practice.

SUBJECTS RANDOMIZED TO CONTROL

Subjects randomized to Control (Additional Sutures) will receive additional dural repair sutures applied immediately to the dural suture line after randomization as deemed necessary by the surgeon. CSF leakage will be evaluated with the Valsalva maneuver 20-25 cm H_2O for 5-10 seconds.

- If watertight closure is not evident after the Valsalva maneuver, the subject will be deemed a failure and the surgeon may revert to his/her standard of care for closure including the use of other commercially available fibrin sealants (except EVICEL®) or an onlay dural patch.

- If watertight closure is achieved but the surgeon feels that an adjunct (excluding the use of fibrin sealants) is required to assure durability of closure then such treatment should be applied. This will be considered a treatment success.

Closure of the remaining layers of the surgical site will be performed according to the surgeon's standard of practice.

TEST PRODUCT: EVICEL® Fibrin Sealant (Human)

STUDY POPULATION: Paediatric subjects, undergoing elective or urgent craniotomy/craniectomy for pathological processes in the posterior fossa (such as benign or malignant tumors, vascular malformation and Chiari 1 malformations) or in the supratentorial region and who were demonstrated to have persistent CSF leakage following primary attempt at suture closure of the dural incision, will be screened and selected from the paediatric patient population of approximately 4-8 clinical sites.

PRIMARY ENDPOINT: Proportion of success (intraoperative watertight closure) in the treatment of intraoperative CSF leakage defined as no CSF leakage from dural repair intraoperatively, during Valsalva maneuver 20-25 cm H_2O for 5-10 seconds.

SECONDARY/SAFETY ENDPOINTS:

- Safety and tolerability assessments
  - Incidence of CSF leakage within 5 days (± 2 days) post-operatively.
  - Incidence of CSF leakage within 30 days (± 3 days) post-operatively.
  - Incidence of adverse events
  - Incidence of surgical site infections (SSI) according to National Healthcare Safety Network (NHSN) criteria within 30 days (± 3 days) post-operatively.

STATISTICAL DESIGN: Sample size of 42 subjects in total is considered adequate to summarize data descriptively. The continuous data will be summarized by number of subjects, mean, median and standard deviation (SD). The categorical data will be summarized by frequency along with associated percentages.

SAMPLE SIZE: The sample size for the study is 42 paediatric subjects, recruited from sites within Europe.

INCLUSION CRITERIA:

Preoperative

1. Patient undergoing elective or urgent craniotomy/craniectomy for pathological processes in the posterior fossa (such as benign or malignant tumors, vascular malformation, and Chiari 1 malformations) or in the supratentorial region and who are demonstrated to have persistent CSF leakage following primary attempt at suture closure of the dural incision;
2. Administration of perioperative antibiotic prophylaxis;
3. Patients who are less than 18 years of age;
4. Patients who are able and willing to comply with the procedures required by the protocol;
5. The subject's parent/legal guardian must be willing to give permission for the subject to participate in the trial, and provide written informed consent for the subject. In addition, assent must be obtained from paediatric subjects who possess the intellectual and emotional ability to comprehend the concepts involved in the trial.

Intraoperative

1. Surgical wound classification Class I (refer to Appendix II). Penetration of mastoid air cells during partial mastoidectomy is permitted;
2. The cuff of native dura along the craniotomy edge on each side is wide enough based on surgeon's judgment to facilitate suturing and to allow for sufficient surface area for adherence of the investigational product.

EXCLUSION CRITERIA:

Preoperative:

1. Subjects with a dura lesion from a recent surgery that still has the potential for CSF leakage;
2. Conditions or treatments significantly compromising the immune system (such as AIDS);

3. Known hypersensitivity to the components (human fibrinogen, arginine hydrochloride, glycine, sodium chloride, sodium citrate, calcium chloride, human thrombin, human albumin, mannitol and sodium acetate) of the investigational product;
4. Hydrocephalus (Occlusive Hydrocephalus is permitted when caused by posterior fossa pathology to be treated, i.e. hydrocephalus is due to blockage caused by a tumor to be removed).
5. Existing CSF (ventricular, etc.) drains, Shunts, Cushing/Dandy cannulation or Burr holes which damage the dura;
6. Female subjects of childbearing potential with a positive urine or serum pregnancy test within 24 hours prior to surgery;
7. Female subjects who are breastfeeding or intend to become pregnant during the clinical study period;
8. Participation in another clinical trial with exposure to another investigational drug or device within 30 days prior to enrollment or expected during the study period;
9. Scheduled or foreseeable surgery within the follow-up period.

Intraoperative:

1. Dura injury during craniotomy/craniectomy that cannot be eliminated by widening the craniotomy/craniectomy to recreate the native dura cuff;
2. Use of implants made of synthetic materials coming into direct contact with dura (e.g., PTFE patches, shunts, ventricular and subdural drains);
3. Planned use of dural patches after primary suture closure of the dura;
4. Placement of Gliadel Wafers;
5. Persistent signs of increased brain turgor;
6. Patient has a gap between durotomy edges of greater than 2mm after primary dural closure.
7. Intersecting durotomy scars in the surgical path from a previous operation that cannot be completely removed by the planned dura resection;
8. Two or more separate dura defects, including defects from ventricular cannulation and ventricular-peritoneal shunting;
9. Major intraoperative complications that require resuscitation or deviation from the planned surgical procedure.

SCHEDULE OF EVENTS

Procedures	**Screening**[1] (within 21 days prior to procedure)	**Baseline** [1] (within 24 hours prior to procedure)	**Surgical Procedure**	**5 Day Visit** (±2 days)	**30-Day Follow Up** (±3 days)
Inclusion/ Exclusion	**X**	**X**	**X**		
Informed Consent/Assent (if applicable)	**X**				
Demographics	**X**				
Medical History	**X**				
Concomitant Medications		**X**	**X**	**X**	**X**
Physical Exam	**X**			**X**	**X**
Laboratory tests (electrolytes, creatinine, full blood count (FBC), liver function test (LFT)		**X**		**X**	
Pregnancy Tests (if applicable)		**X**			
Sutured Dural Closure			**X**		
Randomization			**X**		
Treatment Application			**X**		
Valsalva Maneuver			**X**		
Surgical Site Assessment				**X**	**X**
CSF Leakage Assessment				**X**	**X**
Surgical Site Infection Assessment				**X**	**X**
Wound Healing Assessment				**X**	**X**
Adverse Events			**X**	**X**	**X**

[1]. Screening visit and baseline visit may be combined.

1. INTRODUCTION

Many neurosurgical procedures require that the surgeon pass through the dura mater to gain access to the neural elements, which constitute the central nervous system. Despite advances in neurosurgical techniques and the development of adjunctive methods to repair dura mater defects, cerebrospinal fluid (CSF) leakage is one of the most challenging and potentially dangerous complications of cranial surgery. Meticulous dural repair should include an intraoperative "watertight" closure as the first line of protection from post-operative CSF leakage. CSF leaks can lead to other serious complications like meningitis and delayed wound healing.

Following cranial neurosurgical procedures (craniotomy or craniectomy) that require a dural incision, current dural closure techniques to obtain an intraoperative watertight closure include but are not limited to:

1. Primary suture closure of the durotomy

2. Augmentation or onlay patching of the dural incision with synthetic or tissue-based patches

3. Adjunctive use of various products (prophylactically or to treat persistent CSF leak after primary suture closure)

    a. Additional repair suture

    b. Synthetic Sealants (e.g. polyethylene glycol,etc)

    c. Biological Sealants (e.g fibrin sealants, glutaraldehyde crosslinked bovine albumin)

    d. Autologous tissue buttresses or duroplasty (e.g. fat, muscle, per cranium, etc.)

    e. Gelatin pads or other resorbable biomaterials

Fibrin sealants have been widely used for various neurosurgical indications, in particular as an adjunct to dura repair, in Europe and Japan for more than 20 years. While there has been no concern about safety, there is surprisingly little scientifically derived evidence of their efficacy. A limited number of retrospective studies with historical controls are available from the literature and they give promising results in term of clinical efficacy.

Fibrin sealants are typically derived from biologic sources consisting of blood coagulation factors (i.e. thrombin and fibrinogen) and may include anti-fibrinolytic agents. They are surgical hemostats and wound support products. Their main role is to mimic the final step in the coagulation pathway to form a stable, physiological fibrin clot that assists in healing.

EVICEL® is manufactured by Omrix Biopharmaceuticals Ltd., Israel a subsidiary of Ethicon, a Johnson and Johnson Company and is approved for marketing in the European Union (EU), the United States (US) and in various other countries. In the EU, EVICEL® is approved for use in adults as a supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of hemostasis. EVICEL® is also indicated in adults as suture support for hemostasis in vascular surgery and for suture-line sealing in dura-mater closure. In the US, the approved indication is as an adjunct to hemostasis for use in patients undergoing surgery, when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.

EVICEL® was approved in the US in June 2006 as a manufacturing supplement to the CROSSEAL BLA (BLA # 1603), at which time the proprietary name was changed to EVICEL®. CROSSEAL was previously launched in the US in 2003.

EVICEL® was approved in the EU via the Centralized Procedure in October 2008 (license numbers: EU/1/08/0473/001, EU/1/08/0473/002 and EU/1/08/0473/003 for 1mL, 2mL and 5mL kit respectively).

EVICEL® is a human plasma derived fibrin sealant consisting of two components: (1) Biologically Active Component 2 (BAC2), a concentrate of human clottable protein containing mainly fibrinogen. (2) Human Thrombin. The sealant components are administered to the surgical site by spraying or dripping using a single use applicator device. The applicator device consists of two syringes connected by a syringe holder and bridge. The syringes are linked to a tri-lumen catheter via a closed-system vial-transfer device. A tube with a 0.2 μm bacteriological filter is included to supply CO2 to the device to aerosolize EVICEL® for application by spray if utilising the pressure regulator. Additional accessory tips are also available separately including an airless spray accessory which does not require a pressure regulator for spraying.

The safety and haemostatic efficacy of CROSSEAL/QUIXIL and EVICEL® has been investigated in 10 clinical trials in different clinical settings (retroperitoneal or intra-abdominal, liver, orthopedic and vascular surgery). Information from these clinical studies indicated no particular safety concerns.

EVICEL® has also been developed for use in suture support in neurosurgery and surgical procedures where contact with cerebrospinal fluid or dura mater can occur.

The safety and efficacy of EVICEL® has been demonstrated in nonclinical pharmacology and toxicology studies for the new proposed indication.

A study in a canine model of durotomy repair (Study #08-0002) was conducted to assess the efficacy and safety of EVICEL® in preventing cerebrospinal fluid leakage when compared to another fibrin sealant Tisseel® (which is approved in the UK for use as a sealant in neurosurgery) and Duraseal®, a synthetic surgical sealant approved in the EU and US as a medical device for use an adjunct to sutured dural repair during cranial surgery. The study concluded that EVICEL® was similarly efficacious in preventing cerebrospinal fluid leakage when compared to Tisseel® and Duraseal® sealants in this model. There was no clinically or pathologically apparent CSF leakage observed postoperatively in any group.

Additionally, the local tolerance and the neurotoxicity of EVICEL® were evaluated following a single subdural application in 3 groups of 10 female New Zealand white rabbits (Study No.23597). There were no abnormal clinical or neurobehavioral signs indicating an adverse effect of EVICEL®.

Furthermore, a randomized controlled study was designed to evaluate the safety and effectiveness of EVICEL® as an adjunct to sutured dural repair (Study 400-09-001). The study was initiated in 2010 and completed (last subject last visit in 2011 with investigator sites within the European Union, Australia and New Zealand. This study demonstrates that EVICEL® is safe, that it is effective as an adjunct to primary dural sutures to provide watertight closure of the dura mater and that it is superior to suture repair.

The results of study 400-09-001 were submitted to the European Medicines Agency (EMA) for a Type II variation of the currently approved indication for EVICEL®. On July 26th 2013 the European Commission has issued a decision to approve a variation to the terms of the Marketing Authorization for EVICEL® to include an expanded indication. The indication for EVICEL in the EU specifically relating to neurological procedures will state “for suture-line sealing in dura-mater closure.”

2. STUDY OBJECTIVES

The objective of this study is to evaluate the safety and efficacy of EVICEL®, for suture-line sealing in dura-mater closure to obtain intraoperative watertight closure, in paediatric patients undergoing elective or urgent cranial neurosurgery.

The primary efficacy endpoint will be the proportion of success (intraoperative watertight closure) in the treatment of persistent intraoperative CSF leakage following primary suture repair. Intraoperative watertight closure will be defined as no CSF leakage from the dural repair intraoperatively following the randomly assigned treatment with EVICEL® or Control (additional dural sutures), as assessed during a Valsalva maneuver 20-25 cm H_2O for 5-10 seconds.

The secondary/safety endpoints include:

- Safety and tolerability assessments
    - Incidence of CSF leakage within5 days (± 2 days) post-operatively.
    - Incidence of CSF leakage within 30 days (± 3 days) post-operatively.
    - Incidence of adverse events
    - Incidence of surgical site infections (SSI) according to National Healthcare Safety Network (NHSN) criteria within 30 days (± 3 days) post-operatively.

3. OVERVIEW OF STUDY DESIGN

This is a prospective, randomized, open-label, multi-center controlled study evaluating the safety and effectiveness of EVICEL® as an adjunct to sutured dural closure compared to standard adjunctive dural closure techniques using additional repair sutures only to obtain an intraoperative watertight dural closure. Subjects will be screened and selected from the patient population of approximately 4-8 clinical sites.

Subjects will undergo an elective or urgent posterior fossa or supratentorial procedure (craniectomy or craniotomy). Upon completion of the primary sutured dural repair, the closure will be evaluated for intraoperative CSF leakage with a baseline Valsalva maneuver 20-25 cm H_2O for 5-10 seconds. If a spontaneous leak is apparent immediately after dural closure, no Valsalva will be performed. Subjects who have an identified CSF leak (spontaneous or as identified with the Valsalva) will be enrolled into the study.

Subjects will be randomized to either EVICEL® Fibrin Sealant (Human) or to adjunctive dural closure techniques using Additional Sutures only (Control) in a 2:1 allocation ratio and will be stratified by surgical procedure, posterior fossa or supratentorial.

Subjects will be followed post-operatively through discharge and for 30 days (±3) post-surgery. The incidence of CSF leaks will be assessed within 5 days (±2 days) and 30 days (±3 days) post-operatively as detected by any of the following: clinical observation, diagnostic testing or the need for surgical intervention to treat a CSF leak or pseudomeningocele.

4. STUDY POPULATION

4.1 General Considerations

The specific inclusion and exclusion criteria for enrolling subjects in this study are described in the following sections. The Investigator is expected to invite all subjects meeting the study entry criteria to participate in the study.

4.2 Inclusion Criteria

Preoperative

1. Patient undergoing elective or urgent craniotomy/craniectomy for pathological processes in the posterior fossa (such as benign or malignant tumors, vascular malformation, and Chiari 1 malformations) or in the supratentorial region and who are demonstrated to have persistent CSF leakage following primary attempt at suture closure of the dural incision;
2. Administration of perioperative antibiotic prophylaxis;
3. Patients who are less than 18 years of age;
4. Patients who are able and willing to comply with the procedures required by the protocol;
5. The subject's parent/legal guardian must be willing to give permission for the subject to participate in the trial, and provide written informed consent for the subject. In addition, assent must be obtained from paediatric subjects who possess the intellectual and emotional ability to comprehend the concepts involved in the trial.

Intraoperative

1. Surgical wound classification Class I. Penetration of mastoid air cells during partial mastoidectomy is permitted;
2. The cuff of native dura along the craniotomy edge on each side is wide enough based on surgeon's judgment to facilitate suturing and to allow for sufficient surface area for adherence of the investigational product.

4.3 Exclusion Criteria

Preoperative

1. Subjects with a dura lesion from a recent surgery that still has the potential for CSF leakage.
2. Conditions or treatments significantly compromising the immune system (such as AIDS);
3. Known hypersensitivity to the components (human fibrinogen, arginine hydrochloride, glycine, sodium chloride, sodium citrate, calcium chloride, human thrombin, human albumin, mannitol and sodium acetate) of the investigational product;
4. Hydrocephalus (Occlusive Hydrocephalus is permitted when caused by posterior fossa pathology to be treated, i.e. hydrocephalus is due to blockage caused by a tumor to be removed);
5. Existing CSF (ventricular, etc.) drains, Shunts, Cushing/Dandy cannulation or Burr holes which damage the dura.
6. Female subjects of childbearing potential with a positive urine or serum pregnancy test within 24 hours prior to surgery;
7. Female subjects who are breastfeeding, pregnant, or intend to become pregnant during the clinical study period;
8. Participation in another clinical trial with exposure to another investigational drug or device within 30 days prior to enrollment or expected during the study period;
9. Scheduled or foreseeable surgery within the follow-up period.

Intraoperative

1. Dura injury during craniotomy/craniectomy that cannot be eliminated by widening the craniotomy/craniectomy to recreate the native dura cuff;
2. Use of implants made of synthetic materials coming into direct contact with dura (e.g., PTFE patches, shunts, ventricular and subdural drains);
3. Planned use of dural patches after primary suture closure of the dura;
4. Placement of Gliadel Wafers;
5. Persistent signs of increased brain turgor;
6. Patient has a gap between durotomy edges of greater than 2mm after primary dural closure.
7. Intersecting durotomy scars in the surgical path from a previous operation that cannot be completely removed by the planned dura resection;
8. Two or more separate dura defects, including defects from ventricular cannulation and ventricular-peritoneal shunting;
9. Major intraoperative complications that require resuscitation or deviation from the planned surgical procedure.

5. RANDOMIZATION

5.1 Overview

Randomization will be used to avoid bias in the assignment of treatment to each subject to increase the likelihood that attributes of the subject are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

5.2 Procedures

ETHICON will provide each site with computer-generated randomization envelopes, each bearing the subject randomization number, and containing the treatment allocation. Treatment will be assigned randomly to each subject on a 2:1 basis to either EVICEL® or adjunctive repair sutures only.

In the event that a potential subject fails intraoperative criteria, and is not randomized to the study, the unused randomization envelope should be returned to the series, and used for the next subject.

Given the difference between the two treatment groups, it will not be possible for the surgeon to be blinded to the treatment. However, to avoid any bias in the conduct of the surgical procedure, randomization should only take place after sutured dural closure and the detection of CSF leakage.

6 INVESTIGATIONAL PRODUCT AND CONTROL GROUP

6.1 EVICEL® (Treatment Group)

6.1.1 Formulation

EVICEL® is a human plasma-derived fibrin sealant. EVICEL® consists of two components: a concentrate of Human clottable protein containing mainly fibrinogen (referred to as Biological Component 2; BAC2) and a stabilized solution of Human Thrombin, which incorporates calcium. No material of animal origin is present in the product.

A purpose-designed application device is used to apply EVICEL® to the surgical site by spraying or dripping and has been designed to ensure even mixing of the two components.

Composition of EVICEL®

	Human Fibrinogen	**Human Thrombin**
Active Ingredient	Concentrate of human clottable protein containing mainly fibrinogen	Human thrombin
Other Ingredients	Arginine hydrochloride, Glycine, Sodium chloride, Sodium citrate, Calcium chloride, Water for injection (WFI)	Calcium chloride, Human albumin, Mannitol, Sodium acetate, Water for injection (WFI).

In this study 2ml kits (1ml vial of Fibrinogen & 1ml vial of thrombin) will be provided to investigators.

6.1.2 Labelling and Packaging

The investigational product will have two vials and a Package Leaflet contained within a single box. The product will be labelled according to local regulatory requirements and may contain the following information:

- Name and address of manufacturer / sponsor
- Protocol number
- Lot/Batch number
- Expiry date
- EudraCT number
- Storage conditions
- Statement that the product is limited for clinical trial use only

6.1.3 Shipping, Handling and Storage Conditions

Distribution of EVICEL® kits to the clinical sites will be performed by a qualified person (QP) or appropriate distribution center with proper inventory and quality control capabilities once all the necessary documentation and approvals are obtained.

The two components of the EVICEL® Kit are frozen, and must be stored at –18°C or colder. EVICEL® will be shipped to each site on dry ice during which the temperature will be monitored continuously. Once at the site, the product will be stored in a freezer at –18°C or colder.

The application devices will be shipped and stored at ambient temperature.

6.1.4 Application Device

The application device is commercially available in the US, Canada and several European countries. It is not considered as an investigational product. Depending on its regulatory status, the product will be labelled according to local regulatory requirements, and may contain the following information:

- Name and address of manufacturer
- Protocol number
- Statement that the product is limited for clinical trial use only

6.1.5 Accessory Tips

The accessory tips are commercially available in the US, Canada and several European countries. They are not considered as an investigational product. Accessory tips provided for use with the application device when the tip commercially available in the appropriate country including:

- Standard yellow tip (provided with application device)
- 4 cm Control Tip
- Airless Spray Accessory

Any tip may be used, according to surgeon preference. Tips will be used in accordance with their Product Assembly Guide and Investigator Brochure.

6.1.6 Pressure Regulators

The pressure regulators may be provided when commercially available. They will be used according to the investigator brochure and are not considered as an investigational product.

6.1.7 Preparation

The two frozen components of EVICEL® (BAC2 and Thrombin) must be thawed before use, using one of the following methods:

- 2-8°C (refrigerator): vials thaw within one day; or
- 20-25°C (room temperature): vials thaw within one hour; or
- 37°C; vials thaw within ten minutes and should not be left at 37°C for more than 10 minutes. The temperature must not exceed 37°C.

Thawed, unopened vials must be stored, at the temperature range stated within the Investigator Brochure. Thawed vials must not be re-frozen. Vials thawed at room temperature or above should be used within 24 hours and not returned to refrigerated storage.

Before use, the product must reach 20-30°C.

After thawing, preparation of the product must occur in a sterile surgical field. The two components should be drawn into the application device, following directions enclosed in the application device package. Both syringes must be filled with equal volumes, and should not contain air bubbles. Selection of the appropriate application tip will be left to the discretion of the surgeon.

6.1.8 Dose, Route and Duration of Administration

For each subject, at least one kit of EVICEL® (BAC2 and Thrombin) will be thawed and available for administration prior to randomization. EVICEL® will be sprayed or dripped onto the tissue to produce a thin, even layer. A cure time of 1-2 minutes should be allotted between applications to allow for polymerisation. The amount of EVICEL® required depends upon the area of tissue to be treated and the method of application.

Application can be made by dripping or spraying in accordance with the EVICEL® Investigator Brochure, Accessory Tip Directions and Device and Pressure Regulator Instructions for Use.

6.2 Investigational Product Dispensation and Accountability

A dispensing log will be kept by the designated study personnel. This log will contain information on the date of administration, subject ID and quantity of EVICEL® dispensed, details of any remaining product, and subsequent destruction. The study monitor will verify these logs during the course of the study.

6.3 Additional Sutures Only (Control Group)

Subjects randomized to control will receive additional dural repair sutures as deemed necessary by the surgeon to attempt to achieve a watertight closure.

6.4 Concomitant Medications

6.4.1 Topical Hemostats

The use of flowables, other fibrin sealants, and topical absorbable hemostats such as SURGICEL® will be permitted for hemostasis of the brain and must be used according to their labelling and the surgeon's usual practice.

6.4.2 Documentation of Concomitant Medications

Indication and start-stop dates of concomitant medications administered from 24 hours prior to surgery up to the follow up contact or evaluation will be recorded.

Anesthetics used for surgery and over the counter (OTC) drugs (except for prophylactic aspirin, which should be documented) will not be recorded as concomitant medication except when used to treat an adverse event.

7 STUDY EVALUATIONS

7.1 Study Procedures

The schedule of events included in the synopsis summarizes the frequency and timing of the study procedures. Data collected for the subject during the study will be recorded in the subject's medical records, and study worksheets or source documents, as appropriate, and recorded into the eCRF.

7.1.1 Screening (Within 21 Days Prior to Surgical Procedure)

Prospective subjects will be screened within 21 days prior to surgery. Prior to any study related procedures, subjects will be fully informed of all aspects of the study. Subjects or subject legal representative/parent will be asked to sign a Consent Form. Assent process will also occur when applicable.

The following tests and procedures will be performed at the screening visit. The timing of when these activities may occur will be based on routine hospital practice; The Screening Visit may be combined with the Baseline visit.

- Informed consent & assent process as applicable.
- Allocation of screening number.
- Documentation of demography (age, gender, race, ethnic origin).
- Physical examination, including documentation of relevant medical and surgical history.
- Review of Inclusion / Exclusion criteria to confirm subject eligibility.

7.1.2 Baseline Assessments (Within 24 Hours Prior to Procedure)

The following activities will be performed within 24 hours prior to the procedure:

- Review of inclusion / exclusion criteria to confirm subject eligibility. In the event that a subject is not eligible, the reason will be documented.
- Laboratory tests: electrolytes, creatinine, full blood count (FBC), liver and function test (LFT).
- Serum or urine pregnancy test (if necessary).
- Document all concomitant medications during 24 hours prior to surgery. (see Section 6.4)
- Document any changes in medical history from the screening visit.

7.1.3 Surgical Procedure

The surgeon will use his/her standard surgical techniques for the surgical procedure. The following activities will be performed, and information will be collected, during the surgical procedure:

- Details of procedure including:
  - Operative Procedure (for example: Craniotomy or Craniectomy)
  - Type of procedure (for example: Posterior fossa or Supratentorial)
  - Length of procedure (from first incision to closure completed); and
  - Time in Operating Room (OR) (time subject entered OR and time subject exited OR).
- Intraoperative confirmation of eligibility
- Primary sutured dural closure (use of a tissue based patch autologous/ non-autologous is permitted)

Randomization Procedures:

- EVICEL® will be prepared and available in the sterile field in the operating room, ready for administration for each subject.
- If the subject is randomized to additional sutures, the unused EVICEL® treatment product **MUST** immediately be removed from the sterile field and placed for destruction. After the procedure, accountability of the product should be documented.
- Upon completion of the primary sutured dural repair, the closure will be evaluated for intraoperative CSF leakage. If a leak is present the subject will be randomized into the study. If a spontaneous leak is not present following primary suture repair the closure will be tested with a baseline Valsalva maneuver 20-25 cm H_2O for 5-10 seconds.
- Subjects who have a CSF leak (spontaneous or upon Valsalva) will be randomized into the study.
- The subject will be randomized immediately upon proper identification of a leak by opening the appropriate randomization envelope.

Treatment application:

- **Subjects Randomized to EVICEL**
  For subjects randomized to receive EVICEL® Fibrin Sealant (Human), a thin layer will be applied to the entire length of the suture line and the adjacent area to at least 5mm away, including all suture holes.

If necessary, a second layer of EVICEL® may be applied. A cure time should be allotted between layers to allow for polymerization. CSF leakage will be evaluated with the Valsalva maneuver 20-25 cm H_2O for 5-10 seconds. Application technique, spray or dripping, will be determined by surgeon preference. Method of application will be recorded.

If CSF leakage is still apparent a second treatment (up to two layers) with EVICEL® may be applied. CSF leakage will be re-evaluated with the Valsalva maneuver 20-25 cm H_2O for 5-10 seconds.

If watertight closure is not evident after this second Valsalva maneuver, the subject will be deemed a **failure** and the surgeon may revert to his/her standard of care for closure including the use of other commercially available fibrin sealants (except EVICEL®) or an onlay dural patch.

If watertight closure is achieved with EVICEL®, no additional adjunct should be used and the subject will be deemed a **treatment success**.

Closure of the remaining layers of the surgical site will be performed according to the surgeon's standard of practice.

- **Subjects Randomized to Additional Sutures (Control Group)**
  Subjects randomized to control will receive additional dural sutures as deemed necessary by the surgeon. CSF leakage will be evaluated with the Valsalva maneuver 20-25 cm H_2O for 5-10 seconds.

  If watertight closure is not evident after the Valsalva maneuver, the subject will be deemed a **failure** and the surgeon may revert to his/her standard of care for closure including the use of other commercially available fibrin sealants (except EVICEL®) or an onlay dural patch.

  If watertight closure is achieved but the surgeon feels that an adjunct (excluding the use of fibrin sealants) is required to assure durability of closure then such treatment should be applied. This will be considered a **treatment success**.

  Closure of the remaining layers of the surgical site will be performed according to the surgeon's standard of practice.

- Adverse events (from time of randomization) will be collected

- Concomitant medications will be collected

7.1.4 5 Day Visit (±2 days)

Within 5 days (±2 days) post surgery, the following procedures will be performed and data will be recorded:

- Physical examination

- Laboratory tests: electrolytes, creatinine, full blood count (FBC), and liver function test (LFT).

- Surgical site assessment: infections will be evaluated according to the criteria listed in Appendix 1.

- Wound healing assessment & Incidence of CSF leakage
- Changes in concomitant medications.
- Date of hospital discharge (if not know at visit, captured when known)
- Adverse events.

7.1.5 30 Day Follow-Up Visit (±3 days)

The following information will be recorded at the follow-up visit within 30 days following surgery:

- Physical examination
- Surgical site assessment: infections will be evaluated according to the criteria listed in Appendix 1.
- Wound healing assessment & Incidence of CSF leakage
- Changes in concomitant medications
- Adverse events.

7.2 Procedures for Handling Biological Samples

7.2.1 Laboratory Tests

All laboratory investigations will be performed at each local hospital laboratory. The volume of blood to be taken will be determined according to the standard practices of each hospital. The normal reference ranges and laboratory accreditation certificates must be provided to ETHICON.

7.2.2 Premature Withdrawal of Subjects for the Study

Every enrolled subject should be encouraged to remain in the study until they have completed the follow-up visit. Subjects may discontinue participating in the study at any time and for any reason. However, if the subject decides to discontinue participating in the study, the reason must be documented when possible. Reasons for early withdrawal include, but are not limited to:

- Consent withdrawn by the subject;
- Subject refusal to complete study visits and/or procedures;
- Lost to follow-up: a certified letter will be sent to the subject at their last known address, after a minimum of three attempts to reach the subject by telephone have failed. If communication via certified letter is unsuccessful, the subject will be considered lost to follow-up.

Subjects who discontinue from the study prematurely will not be replaced.

8 STATISTICAL METHODS

The Biostatistics groups of Clinical Development at Johnson and Johnson Global Surgery Group will be responsible for the overall analysis of data from this protocol. The detailed Statistical Analysis Plan (SAP) will be based on and will supplement the statistical design and analysis described in this section.

8.1 Sample Size Determination

The sample size required for the trial is 42 randomized Subjects. This sample size is considered adequate by EMA Paediatric Investigation Plan to summarize the data descriptively. The continuous data will be summarized by number of subjects, mean, median and standard deviation (SD).

8.2 Planned Analyses

8.2.1 Analysis Sets

In all cases, treatment allocation will be based on randomisation. If more than two subjects are mis-randomized, then an additional analysis based on treatment received will be used for confirmatory analyses for all effectiveness endpoints.

Three analysis sets are defined:

- The Safety Set will contain all subjects who received treatment.
- The Full Analysis Set (FAS) will contain all randomized subjects (equivalent to the Intent-to-Treat [ITT] set).
- The Per Protocol Set will contain subjects in the FAS who have no major protocol deviations affecting the primary endpoint (these will be agreed before database lock).

8.3 Effectiveness

The following will be analyzed using the FAS and Per Protocol Set:

- Proportion of success (intraoperative watertight closure) in the treatment of intraoperative CSF leakage defined as no CSF leakage from dural repair intraoperatively, during Valsalva maneuver 20-25 cm H2O for 5-10 seconds.

The primary analysis will use the FAS for proportion of successes. The Per Protocol analysis will be considered confirmatory.

8.3.1 Methods of Analysis

The continuous data will be summarized by number of subjects, mean, standard deviation (SD), minimum and median and maximum. The categorical data will be summarized by frequency along with associated percentages. In addition, two sided 95% CI will be reported for ratio of the proportion of success in the EVICEL treated subjects/the proportion of success in Control subjects

8.4 Safety/Secondary Endpoints

8.4.1 Safety/Secondary Endpoints Variables/Criteria

The following will be summarized using the Safety Set:
Safety and tolerability assessments:

- Adverse events

- Laboratory tests
- Incidence of CSF leakage within 5 days (± 2 days) post-operatively.
- Incidence of CSF leakage within 30 days (± 3 days) post operatively.
- Incidence of adverse events (including CSF leaks, pseudomeningocele formation, etc.)
- Incidence of surgical site infections (SSI) according to National Healthcare Safety Network (NHSN) criteria within 30 days (± 3 days) post-operatively.

8.4.2 Methods of Analysis

Adverse events will be summarised descriptively by the treatment received, using Medical Dictionary for Regulatory Activities (MedDRA) terminology. Coagulation parameters (baseline and post-surgery samples) will use SI units.

Laboratory values will be reported in International System (SI) units. Values and changes from baseline will be listed but not summarised. Clinically significant changes will be reported as part of the AE summary.

8.5 Handling of Missing Data

It is not anticipated that there will be any data missing for treated subjects for the primary endpoint, but if there is, missing data will be considered failures for the primary analysis. Confirmatory analyses will be performed considering missing data as successes, and also, worst-case (with missing data for the EVICEL® group considered failures and missing data for the Control group considered successes).

Analyses of secondary endpoints consider missing data as failures.

9 ADVERSE EVENTS

9.1 Adverse Event

An adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a drug, without any judgment about causality. Since post operative pain is an expected outcome of this type of surgery, for purposes of this study, only exacerbations of expected post operative pain based on the Investigator's judgment should be reported as an AE.

The Investigator may also need to consider whether an adverse event is attributable to the application device, based on any of the following:

- Resulting from insufficiencies or inadequacies in the IFU
- In the actual use of the application device, tips or regulator
- The result of user error

9.2 Suspected adverse reaction

A suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction.

9.3 Adverse reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

9.4 Serious Adverse Event

A ”serious” adverse event (SAE) is any untoward medical occurrence that, in the view of either the investigator or sponsor, it:

- Results in death;
- Is considered to be life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability, incapacity or substantial disruption of the ability to conduct normal life functions;
- Results in a congenital anomaly or birth defect;
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.4.1 Life threatening

Life threatening refers to an adverse event or suspected adverse reaction in which, in the view of the investigator or sponsor, the subject was at immediate risk of death at the time of the event; it does not include an event that might have caused death if it were more severe.

9.4.2 Hospitalizations

Any event requiring inpatient hospitalization (or prolongation of hospitalization) that occurs during the course of a subject’s participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

- Social reasons in absence of an adverse event;
- Surgery or procedure planned before entry into the study (must be documented in the CRF).

9.4.3 Unexpected

An adverse event or suspected adverse reaction is considered ‘‘unexpected’’ if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, though they are mentioned as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, they are not specifically mentioned as occurring with the particular drug under investigation.

9.4.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A suspected unexpected serious adverse reaction (SUSAR) is a suspected adverse reaction that is both serious and unexpected.

9.5 Relationship

The relationship of the investigational product to an adverse event must be determined using the following classification based on the information on the Investigator Brochure:

None: No relationship with investigational product.

Possible: Reasonable possibility that the event was caused by the investigational product.

Related: The event was certainly or probably caused by the investigational product.

9.6 Severity

The following definitions should be used to determine the severity rating of all AEs:

Mild: Awareness of signs or symptoms, but these are easily tolerated and are transient and mildly irritating only. There is no loss of time from normal activities and symptoms do not require medication or a medical evaluation.

Moderate: Discomfort enough to cause interference with usual activities or require therapeutic intervention, such as concomitant medication.

Severe: Incapacity with inability to work or do usual activities.

9.7 Collection of Adverse Events

AEs will be recorded as they are reported, whether spontaneously volunteered or in response to questioning about well-being. AEs will be collected from the point of randomization during the surgical procedure, throughout the hospital admission, and until completion of the 30-day follow-up visit.

All AEs will be documented in the subject's source documents (e.g. medical records) and eCRF. All AEs will be followed until completion of the 30-day follow-up visit or until a stable resolution, whichever is sooner.

Details of all AEs occurring during the study must be recorded on the AE form with the following information:

- Description of the event
- Dates of onset and resolution
- Severity
- Action taken
- Outcome
- Relationship to investigational product
- Whether the AE is serious or not

Expectedness of an SAE will be defined based on whether the specificity or severity of which is not consistent with the current investigator brochure.

Other: The investigator may also need to consider whether an event is attributable to the investigational product, based on insufficiencies or inadequacies in the instructions for use or as a result of user error. The investigator must contact the Sponsor should this occur.

9.8 Adverse Event Reporting

It is a requirement that the Investigator promptly reports all SAEs (irrespective of relationship) to [redacted] as soon as possible, but no later than 24 hours after becoming aware of the event occurring.

SAE reports must be communicated as follows:
Attn: Medical Monitor

[redacted]	[redacted]
[redacted]	[redacted]

Suspected, unexpected serious adverse drug reactions (SUSARs) will be reported to the FDA, all relevant competent authorities, and IRBs/Ethics Committees within the required timeframes of seven calendar days for SUSARs that are fatal or life-threatening, and fifteen calendar days for all other SUSARs by the Sponsor.

All other Adverse Events (AEs) must be reported (entered) into the RAVE EDC clinical trial database (electronic case report form (eCRF) within two weeks from the date the site becomes aware of the AE.

10. DEVICE COMPLAINT HANDLING

If a device failure occurs with the applicator device, tips or regulators, a Device Complaint Form must be completed and faxed immediately (within 24 hours to [redacted]. Included are those complaints related to the applicator devices, tips or regulators that have been open but unused (e.g. sterile container was opened inadvertently). Upon receipt of the Complaint Form, instructions will be given on handling/returning of the defective device.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

Prior to participation, the study procedures and any known or likely risks will be explained to the subjects (as applicable) and/or their parent or legal guardian by the investigator or other qualified study personnel. An Informed Consent Form and patient information leaflet, as applicable, will also be provided containing all the required information. Any questions will be answered and the patient and/or their parent or legal guardian will then be given sufficient time to consider their participation in the study before signing a consent form. For paediatric subjects who possess the intellectual and emotional ability to comprehend the concepts involved in the trial, must also give their assent to participate in the study. An age appropriate patient leaflet/assent will be provided. Subjects and/or their parent or legal guardian should receive a copy of the Informed Consent Form.

The Investigator (or designee) will explain that the subjects and/or parent or legal guardian are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify.

Each subject and/or their parent or legal guardian will be informed that the subject's source medical records may be checked by representatives from the Sponsor or from a regulatory agency, in accordance with applicable regulations. However, they should be made aware that all information will be treated with confidentiality, and a study ID code or number will identify them.

11.2 Investigational Review Boards / Ethics Committees

The investigator must submit the Protocol and the Consent Form to the appropriate IRB/EC according to local requirements. Approval from the IRB/EC must be obtained prior to starting any study-related procedure.

12 Data Management

12.1 Electronic Data Capture (EDC)

An EDC system will be utilized by trial site personnel to transfer trial data from source records (medical records and/or source document worksheets) onto common eCRFs (electronic Case Report Forms). This system is a web-based, secure electronic software application. This system was designed and is developed and maintained by [redacted] in a manner that is compliant with national and international GCP data protection/data privacy and electronic record/electronic signature (e.g., 21 CFR Part 11) regulatory requirements. The EDC system will be used to facilitate the collection of all trial data at the site. Designated site personnel will be responsible for entering patient data into the EDC system. All external and Sponsor internal users will be trained on the EDC application at a level dependent on their planned function. An EDC digital User Manual will be available under the help menu within the [redacted] website to assist in the collection and entry of source data into the electronic casebook. A 24/7/365 Help Desk Support line staffed by the outsourced vendor will be available to respond to site and monitor questions.

12.2 Data Collection

The Investigator must maintain required records on all study subjects. Data for this study will be recorded in the subject's medical records, study-specific worksheets, and on eCRFs provided by the Sponsor in accordance with the parameters set forth in ICH Topic E6 for GCP (1.5.96) Guidelines – Responsibilities of Sponsor, Monitor, and Investigator and applicable regulations. All data on the CRFs should be recorded from appropriate source documentation.

Each EDC eCRF will be completed by the PI or PI's designee. Every effort should be made to respond to all monitoring and/or data management questions on each eCRF as completion of the data is required by the protocol. A unique ID number will identify each subject. At no time should the subject name appear on the eCRFs. Complete data is needed in order to provide statistical analysis for each subject. All data should be recorded accurately and completely. The investigator is responsible for reviewing and approving each completed eCRF. Assurance of overall review and approval will be documented by the Investigator electronically signing each subject's electronic casebook.

12.3 Data Correction

Required data corrections to eCRFs will be prompted via automated electronic edit checks and/or queries manually created by sponsor reviewers. The change(s), individual making the change(s), and time the change(s) were made to the eCRFs will be automatically captured in the audit trail within [redacted].

12.4 Source Documentation

Investigators must keep accurate separate records (other than the eCRFs) of all subjects' visits, being sure to include all pertinent study related information. A statement should be made indicating that the subjects have been enrolled in Protocol and have provided written Informed Consent. Any and all side effects and adverse events must be thoroughly documented. Results of any diagnostic tests conducted during the study should also be included in the source documentation. Telephone conversations with the subjects concerning the study must also be recorded.

The Investigator is responsible for maintaining a Subject Identification Log, which will include all subjects who provided informed consent (i.e. to include randomized subjects and screening failures). This confidential subject identification code provides the link between named subject source records in the subject file and anonymous eCRF data provided to ETHICON.

The Investigator must retain all study related documentation until at least two years after the final marketing application is approved, or at least two years have elapsed since the formal discontinuation of the clinical study. Study documents should not be destroyed without prior written agreement between the Investigator and ETHICON. The sponsor must be notified if the Investigator wishes to assign the study records to another party, or move them to another location.

13 SPONSOR OBLIGATIONS

13.1 Monitoring

The Sponsor monitor will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the trial. The monitor will visit as soon as possible following enrollment of the first subject and at regular intervals during the study (approximately every four to six weeks) as deemed necessary. It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries. The study monitor will have access to laboratory test reports and any other source records and data needed to verify the entries on the eCRFs, unless restricted by local laws. The Investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.2 Regulatory Requirements

This study will be conducted in accordance with specific provisions of the associated IRB/IECs, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable national and regional regulatory requirement(s).

13.3 Liability and Insurance Conditions

In case of any damage or injury occurring to a subject in association with the trial medication or participation in the study, ETHICON has provided insurance cover. A copy of this policy is on file at ETHICON.

14 INVESTIGATOR OBLIGATIONS

14.1 Audit and Inspection

The Investigator will make source data and documents for this study available to an appropriately qualified quality assurance auditor mandated by ETHICON, or to regulatory authority inspectors, after appropriate notification.

14.2 Confidentiality of Subject Records

The Investigator will ensure that the subjects' anonymity will be maintained. On eCRFs or other study documents submitted to ETHICON, subjects will not be identified by their names, but by an identification code *that may consist of a combination of the site, and randomization or enrollment number*. Documents not for submission to ETHICON i.e. the Subject Identification Log and original subjects' consent forms will be maintained in the Investigator Site File.

14.3 Record Retention

The Investigator will maintain all eCRFs and all source documents that support the data collected from each subject, and all trial documents as specified by applicable regulatory requirement(s). The Investigator will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least 2 years after the last approval of a marketing application worldwide, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with ETHICON. It is the responsibility of ETHICON to inform the Investigator as to when these documents no longer need to be retained. If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. ETHICON must be notified in writing of the name and address of the new custodian.

15 CHANGES TO THE PROTOCOL

15.1 Protocol Amendments

All protocol amendments are required to be submitted for information/consideration to the regulatory authorities, IRBs and ECs.

15.2 Clinical Trial Termination

Both the Investigator and ETHICON reserve the right to terminate the study at any time. Should this be necessary, the procedures will be arranged on an individual study basis after review and consultation with both parties. In terminating the study, ETHICON and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests and safety.

15.3 Use of Information and Publication

All information concerning study data, ETHICON's operations, patent application, formulas, manufacturing processes, basic scientific data, and formulation information, supplied by the Sponsor or Sponsor designee to the investigator and not previously published, is considered confidential and remains the sole property of ETHICON. The Investigator agrees to use this information only to accomplish this study and will not use it for other purposes without the sponsor's written consent.

The Investigator understands that the information developed in the clinical study will be used by ETHICON in connection with the continued development of the EVICEL® product, and thus may be disclosed as required to other clinical investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the sponsor with all data obtained in the study.

Any publication or other public presentation of results from this study requires prior review by ETHICON. Draft abstracts, manuscripts, and materials for presentation at scientific meetings must be sent to the sponsor at least 30 working days prior to abstract or other relevant submission deadlines. Authorship of publications resulting from this study will be based on generally accepted criteria for major medical journals.

The investigator understands not to use the name of ETHICON, EVICEL®, or any its employees, in any publicity, news release or other public announcement, written or oral, whether to the public, press or otherwise, relating to this protocol, to any amendment hereto, or to the performance hereunder, without the prior consent of ETHICON.

ETHICON CONTACT DETAILS

Appendix 1: CDC/NHSN Criteria for Defining a Surgical Site Infection (SSI)

Superficial Incisional SSI

Infections occur within 30 days after the operation *and* infection involves only skin or subcutaneous tissue of the incision *and* at least *one* of the following:

1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture or fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat *and* superficial incision is deliberately open by surgeon, *unless* incision is culture-negative.
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

Do *not* report the following conditions as SSI:

1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration.
2. Infection of an episiotomy or newborn circumcision site.
3. Infected burn wound.
4. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).

Note: Specific criteria are used for identifying infected episiotomy and circumcision site and burn wounds.

Deep Incisional SSI

Infections occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation *and* infection involves deep soft tissues (e.g., fascial and muscles layers) of the incision *and* at least *one* of the following:

1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative.
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

Notes:

1. Report infection that involves both superficial and deep incisional sites as deep incisional SSI.
2. Report organ/space SSI that drains through the incision as a deep incisional SSI.

Organ/space SSI

Infections occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation *and* infection involves any part of the anatomy (e.g., organs or spaces) other than the incision, which was opened or manipulated during an operation *and* at least *one* of the following:

1. Purulent drainage from a drain that is placed through a stab wound into the organ space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histological or radiologic examination.
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

Appendix 2: U.S. Center for Disease Control (CDC) Guideline for Prevention of SSI Surgical Wound Classification

CLASS I/CLEAN:

An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital and urinary tracts are not entered. Clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow non-penetrating (blunt) trauma should be included in this category if they meet these criteria.

CLASS II/CLEAN-CONTAMINATED:

An operative wound in which the respiratory, alimentary, genital and urinary tract is entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.

CLASS III/CONTAMINATED:

Open, fresh, accidental wounds, operations with major breaks in sterile technique or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered.

CLASS IV/DIRTY OR INFECTED:

Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

Appendix 3: Flow Chart for Intra-operative Watertight Dural Closure Assessment during Surgical Procedure