



**A Single-Blinded, Randomized, Controlled Study to Evaluate the Safety and Effectiveness of EVICEL®  
Fibrin Sealant (Human) Compared to a Hydrogel Sealant as an Adjunct to Sutured Dural Repair**

The EVICEL® Neurosurgery Phase III Study

Protocol Number: BIOS-14-002

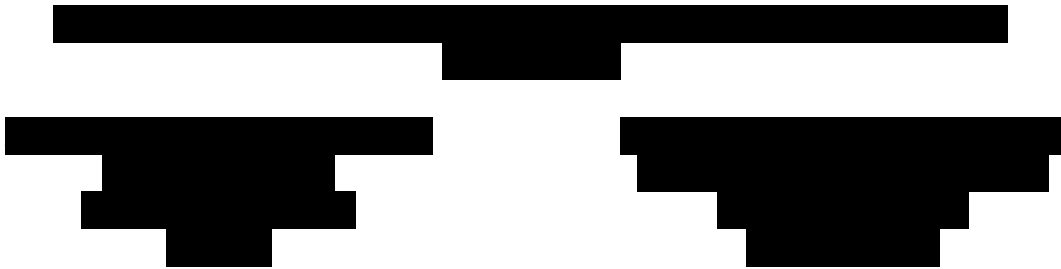
Original Protocol: October 2, 2014

Amendment 1: 12 February 2015

Amendment 2: 17 November 2015

Amendment 3: 16 May 2016

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**COMPLIANCE STATEMENT**

This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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Investigator Agreement:

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

[REDACTED]

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**A Single-Blinded, Randomized, Controlled Study to Evaluate the Safety and Effectiveness of EVICEL® Fibrin Sealant (Human) Compared to a Hydrogel Sealant as an Adjunct to Sutured Dural Repair**

**Synopsis**

**OBJECTIVE:** The objective of this study is to evaluate the safety and efficacy of EVICEL® Fibrin Sealant (Human) for use as an adjunct to sutured dural repair in cranial surgery

**INVESTIGATIONAL PRODUCT:** EVICEL® Fibrin Sealant (Human)

**STUDY DESIGN:** This is a single-blinded, randomized, controlled study evaluating EVICEL® as an adjunct to sutured dural closure compared to DuraSeal™ Dural Sealant System.

Approximately 230 subjects undergoing posterior fossa or supratentorial procedures (craniectomy or craniotomy) will be enrolled in the trial. At least 60 subjects undergoing posterior fossa procedures will be randomized.

Upon completion of the sutured dural repair, the closure will be evaluated for intraoperative cerebrospinal fluid (CSF) leakage with a baseline Valsalva maneuver performed to an intra-thoracic pressure between 20-25 cm H<sub>2</sub>O for 5-10 sec. If a spontaneous leak is apparent immediately after dural closure, no Valsalva maneuver will be performed.

Subjects who have a CSF leak will be stratified by surgical procedure, posterior fossa or supratentorial approach, and then randomized to either EVICEL® Fibrin Sealant or DuraSeal™ Dural Sealant System in a 1:1 allocation ratio.

Subjects will be followed post-operatively through discharge and again at 30 (-/+ 7 days) days and 60 (-/+14) days post-surgery. The incidence of CSF leaks for the primary endpoint will be assessed up to the 30 day post-operative follow-up period. A CSF leak will be reported as detected by any of the following: clinical observation, diagnostic testing, imaging or the need for surgical intervention to directly treat a CSF leak.

**STUDY POPULATION:** Subjects at least 18 years of age undergoing craniotomy or craniectomy surgery for pathological processes in the supratentorial procedures or posterior fossa (such as benign or malignant tumors, vascular and Chiari 1 malformations).

**PROCEDURE:** **Subjects Randomized to EVICEL®**  
For subjects randomized to receive EVICEL®, a thin layer will be applied to cover the entire length of the suture line and the adjacent area to assure



complete coverage of the suture line 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 the EVICEL® clot formation and stabilization. CSF leakage will be evaluated with the Valsalva maneuver performed to an intra-thoracic pressure between 20-25 cm H<sub>2</sub>O for 5-10 sec.

If a 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 as described above.

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

If watertight closure is not evident after the final Valsalva maneuver, the subject will be deemed a failure and surgeon may revert to his/her standard of care for closure, this can include additional treatment with EVICEL® if clinically appropriate. The use of other fibrin sealants is not permitted.

Subjects randomized to EVICEL® may not have their dura treated with DuraSeal™ Dural Sealant System or any other PEG based or fibrin sealants.

#### **Subjects Randomized to DuraSeal™**

For subjects randomized to DuraSeal™, the assigned product will be applied to the entire length of the suture line, including all suture holes, according to the manufacturer's instruction for use. CSF leakage will be evaluated with the Valsalva maneuver performed to an intra-thoracic pressure between 20-25 cm H<sub>2</sub>O for 5-10 seconds.

If a CSF leakage is still apparent, continue treatment with DURASEAL™ per manufactures directions. CSF leakage will be re-evaluated with the Valsalva maneuver as described above. If watertight closure is achieved for DuraSeal™ treatment, no further treatment, including the use of onlays, will be allowed.

If watertight closure is not evident after the final Valsalva maneuver, the subject will be deemed a failure and surgeon may revert to his/her standard of care for closure, this can include additional treatment with DuraSeal™, if clinically appropriate. The use of fibrin sealants is not permitted.

Subjects randomized to DuraSeal™ may not have their dura treated with EVICEL® Fibrin Sealant or any other PEG based or fibrin sealants.

**PRIMARY ENDPOINT:** The primary endpoint is the proportion of subjects that do not have a CSF leak during surgery and up to the 30-day (-/+ 7) post-operative period.

A subject is declared as a success when the following conditions are met:

- absence of intra-operative CSF leak following final Valsalva maneuver, and
- absence of CSF leak or Pseudomeningocele in the surgical area during the 30-day (-/+ 7) follow-up period.

A confirmed CSF leak or pseudomeningocele is diagnosed by physical examination, diagnostic testing, imaging study or the need for surgical intervention to directly treat a CSF leak during the 30-day (-/+ 7 days) follow-up at the location where randomized treatment was applied.

**SECONDARY ENDPOINTS:**

- Incidence of Intra-operative CSF leakage following final Valsalva maneuver.
- Incidence of post-operative CSF leakage within 30 (-/+7) days post-operatively.
- Incidence of post-operative CSF leakage within 60 (-/+ 14) days post-operatively.
- Incidence of adverse events.
- Incidence of surgical site infections (SSI) according to NNIS definition and CDC classification within 30 days (-/+7) post-operatively (See Appendix I and II).

**SAFETY:**

Adverse events will be collected from time of randomization, throughout the 60 day (-/+ 14) follow-up period after the procedure.

**STATISTICAL DESIGN:**

This is a non-inferiority trial using a one-sided alpha 0.025 and 90% power. The assumed success rate in the both arms is 95%.<sup>6,14</sup>

**STUDY HYPOTHESIS:**

The statistical hypothesis for testing the treatment difference is presented as follows:

- $H_0: \Delta \leq -0.10$  tested against the alternative hypothesis
- $H_a: \Delta > -0.10$ .

where:

- $\Delta$  is the difference between the success rates of Experimental and Control (Experimental minus Control)
- -0.10 is the non-inferiority difference
- The assumed proportion of successes for Control is 0.95

$P_C$  is the proportion of success in DuraSeal™ Control subjects and  $P_E$  is the proportion of success in EVICEL® subjects.

**SAMPLE SIZE:**

The number of randomized subjects required for this trial is 202 subjects (101 per treatment arm) from centers in North America, Europe, and Asia-Pacific.

There will be approximately 30 global sites. In order to account for potential missing follow-up information (drop-outs), approximately 230 subjects will be enrolled. At least 60 subjects undergoing posterior fossa procedures will be randomized.

Two hundred and two (202) evaluable subjects (101 per arm) will achieve 90% power to detect a non-inferiority margin difference in group proportions of -0.10. The proportion of successes in the Control group is 0.95. The proportion of successes in EVICEL<sup>®</sup> group is assumed to be 0.85 under the null hypothesis of inferiority. The power was computed for the case when the actual proportion of successes in the EVICEL<sup>®</sup> group is 0.95. The one-sided significance level of the test is 0.025.

If the lower limit of the one-sided 97.5% confidence interval for  $\Delta$  is greater than -0.10, then it will be concluded that Experimental is considered to be non-inferior to Control.

#### **INCLUSION CRITERIA:**

##### **Pre-Operative**

1. Subjects  $\geq 18$  years of age undergoing craniotomy/craniectomy for pathological processes in the supratentorial region or posterior fossa (such as benign or malignant tumors, vascular malformation, and Chiari 1 malformations);
2. Subjects or legally authorized representatives must be willing to participate in the study and provide written informed consent.

##### **Intra-Operative**

1. Surgical wound classification Class I (refer to Appendix II). Superficial penetration of mastoid air cells during partial mastoidectomy is permitted.
2. The cuff of native dura along the craniotomy edge on each side is adequate, based on surgeon's judgment, to facilitate suturing and to allow for sufficient surface area for adherence of the investigational product
3. Presence of intra-operative cerebrospinal fluid (CSF) leakage following primary dural closure or after Valsalva maneuver

#### **EXCLUSION CRITERIA:**

##### **Pre-Operative**

1. Subjects with a cranial dural lesion from a recent surgery that still has the potential for CSF leakage.
2. Chemotherapy within 30-days prior to enrollment or scheduled within 7 days following surgery.
3. Radiation therapy to the head within 30-days prior to enrollment or scheduled within 7 days following surgery.
4. A previous craniotomy/craniectomy within 6 months prior to the study surgery.
5. Known hypersensitivity to the components (such as human fibrinogen, arginine hydrochloride, glycine, sodium chloride, sodium citrate, calcium chloride, human thrombin, human albumin, mannitol and sodium acetate) of the investigational product.
6. Subjects with a known allergy to FD&C Blue #1 dye in DuraSeal

7. Subjects with an infection present at the surgical site
8. Subjects with an infection indicated by any one of the following: clinical diagnosis of infection, fever, positive urine culture, positive blood culture, positive chest X-ray.
9. Female subjects of childbearing potential with a positive pregnancy test or intent to become pregnant during the clinical study period.
10. Female subjects who are nursing.
11. Exposure to another investigational drug or device clinical trial within 30 days prior to enrollment or anticipated in the 60 day follow-up period.
12. Subjects with severely altered renal or hepatic function, with a compromised immune system or autoimmune disease who can NOT receive DuraSeal™.
13. Subjects with penetrating traumatic injuries to the head with damage to the dura.

### **Intra-Operative**

1. Dural injury during craniotomy/craniectomy that cannot be eliminated by widening the craniotomy/craniectomy to recreate the native dural cuff.
2. Patient has a gap between durotomy edges of greater than 2mm after primary dural closure.
3. Approaches that would not allow sutured dural closure such as trans-sphenoidal or trans-labyrinthine-/petrosal/-mastoid. Superficial penetration of mastoid air cells is allowed.
4. Use of implants made of synthetic materials coming into direct contact with dura (e.g., PTFE patches, shunts, ventricular and subdural drains, existing CSF drains).
5. Use of other fibrin sealants or PEG-based sealants on the dural closure. Approved fibrin sealants may be used for hemostasis if not in contact with the dura.
6. Hydrocephalus, except occlusive hydrocephalus caused by posterior fossa pathology or incompletely open cerebrospinal fluid pathways to be treated during the planned surgical procedure.
7. Placement of Gliadel Wafers
8. Intersecting durotomy scars in the surgical path from a previous operation that cannot be completely removed by the planned dural resection.
9. Two or more separate cranial dural defects, including defects from ventricular cannulation and ventriculo-peritoneal shunting
10. Subjects with any other intra-operative findings identified by the surgeon that may preclude the conduct of the study procedure.
11. Confined bony structures where nerves are present where neural compression may result due to swelling.

### Schedule of Events

Procedures	Screening <sup>1</sup> (within 30 days prior to procedure)	Baseline <sup>1</sup> (within 24 hours prior to procedure)	Surgical Procedure	Post-Surgery to Hospital Discharge	30-Day Follow Up (-/+7 days)	60-day Follow Up (-/+14 days) <sup>4</sup>
Inclusion/Exclusion	X	X	X			
Informed Consent	X					
Demographics	X					
Medical History	X					
Concomitant Medications		X	X	X	X	X
Physical Exam	X			X	X	
Laboratory tests		X		X <sup>3</sup>	X	
Pregnancy Tests (if applicable)		X				
Sutured Dural Closure			X			
Randomization			X			
Treatment Application			X			
Valsalva Maneuver			X			
Intra-Operative Details			X			
Perioperative Information <sup>2</sup>			X	X		
CSF Leak Assessment			X	X	X	
Surgical Site Infection Evaluation				X	X	
Wound Healing Assessment				X	X	
Adverse Events			X	X	X	X

1. Screening and Baseline visits can be the same visit as long as all study procedures are completed. At least one set of laboratory tests and pregnancy test are needed within 7-days prior to the procedure.
2. Including but not limited to, Length of stay (ICU and overall LOS),
3. Within 72 hours prior to discharge. Labs taken closest to discharge should be used.
4. 60 day follow-up visit may be in-person or over the phone.

## 1. Introduction

Many neurosurgical procedures require that the surgeon pass through the dura mater to gain access to the neural elements, which constitute part of the central nervous system. Despite advances in neurosurgical techniques and the development of new methods to repair dura mater defects, cerebrospinal fluid (CSF) leakage is one of the most challenging complications of cranial surgery.<sup>1</sup> Meticulous dural repair should include an intraoperative watertight closure as protection from post-operative CSF leakage.<sup>1</sup> CSF leaks can lead to other serious complications like meningitis and delayed wound healing.<sup>1-3</sup>

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 biologic patches
3. Adjunctive use of various products designed for prophylactic use or to treat persistent CSF leak after primary sutured dural closure
  - a. Additional suture repair
  - b. Synthetic Sealants (e.g. polyethylene glycol, etc)
  - c. Biological Sealants, e.g fibrin sealants, glutaraldehyde crosslinked bovine albumin
  - d. Autologous tissue buttresses or duraplasty materials, e.g. fat, muscle, peri-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, for more than 20 years.<sup>4-6</sup> Even though there has been a long history of fibrin sealant use in this area, there is a limited number of multicenter, prospective, controlled randomized clinical studies published. Nevertheless, the published literature does include number of retrospective studies with historical controls and few randomized trials which provide support of clinical efficacy of fibrin sealants in dura mater sealing.<sup>5-6</sup>

Fibrin sealants are typically derived from biologic sources consisting of blood coagulation factors (i.e. thrombin and fibrinogen) and may contain additional components. They are typically marketed as 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.<sup>7</sup>

### **EVICEL® Fibrin Sealant (Human)**

EVICEL® is a fibrin sealant manufactured by Omrix Biopharmaceuticals Ltd., Israel and is approved for marketing in the EU (approved via the Centralized Procedure in October 2008), the US (since 2006) and in numerous other countries worldwide.

EVICEL® is a human plasma derived fibrin sealant consisting of two components: (1) Human Fibrinogen (named also Biologically Active Component 2 (BAC2)).(2) Human Thrombin containing calcium.<sup>8-9</sup> 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 or other available accessory tip device via a closed-system vial-transfer device.

EVICEL's current indication is the following in the US and EU:

*US: EVICEL<sup>®</sup> is a fibrin sealant indicated 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.<sup>8</sup>*

*EU: Supportive treatment in surgery where standard surgical techniques are insufficient, for improvement of haemostasis. Suture support for haemostasis in vascular surgery and for suture line sealing in dura mater closure.<sup>9</sup>*



EVICEL<sup>®</sup>'s EU indication for suture line sealing in dura mater closure was supported by multicenter, prospective, controlled, randomized clinical study which demonstrated EVICEL safe and effective as an adjunct to dural sutures to provide watertight closure of the dura mater in cranial surgery. The study further demonstrated that EVICEL was superior to the control (i.e. adjunctive dural closure techniques using additional repair sutures only) in achieving intra-operative watertight closure of the dura. One hundred and thirty-nine subjects were randomized: 89 to EVICEL and 50 to Control. Intra-operative watertight closure was achieved in 92.1% EVICEL-treated subjects versus 38.0% in the control group; a treatment difference of 54.1% ( $p < 0.001$ ). The treatment differences in the supratentorial and posterior fossa strata were 49.1% and 75.7%, respectively ( $p < 0.001$ ). The incidence of adverse events was similar between treatment groups. No deaths or unexpected serious adverse drug reactions were reported. The CSF leakage from the dural repair site within 30 days post-operatively was 2.2% and 2.0% in EVICEL and control groups, respectively. The clinical study indicated no particular safety concerns in regard to dura mater closure.<sup>6</sup>

### **DuraSeal<sup>™</sup> Dural Sealant System**

DuraSeal<sup>™</sup> Dural Sealant System is a commercially available synthetic sealant that is intended for use as an adjunct to sutured dural repair during cranial surgery to provide watertight closure.

The product is a synthetic absorbable sealant (with applicator) composed of two solutions, a polyethylene glycol (PEG) ester solution and a rilysine amine solution. When these two solutions are mixed together, the precursors cross link to form a hydrogel sealant.

DuraSeal<sup>™</sup> Dural Sealant System is approved in the US (since 2005), EU (since 2003) and numerous countries world-wide. DuraSeal<sup>™</sup>'s current indication is the following in the US and EU:

*US: The DuraSeal Dural Sealant System is intended for use as an adjunct to sutured dural repair during cranial surgery to provide watertight closure.<sup>14</sup>*

*EU: The DuraSeal Sealant System is intended for use as an adjunct to standard methods of dural repair, such as sutures, to provide watertight closure.<sup>15</sup>*

### **EVICEL® Neurosurgery Phase III Study**

This clinical study is a non-inferiority study designed to evaluate the safety and efficacy of EVICEL® for use as an adjunct to sutured dural repair in cranial surgery as compared to DuraSeal™ Dural Sealant System. The study will assess both achievement of intra-operative watertight closure of the dural suture line and the occurrence of post-operative CSF leaks. This study will provide additional data to support the development of EVICEL® for use in tissue sealing and suture support in neurosurgery and surgical procedures where contact with cerebrospinal fluid or dura mater may occur.

## **2. Study Objectives**

The objective of this study is to evaluate the safety and efficacy of EVICEL® Fibrin Sealant (Human) for use as an adjunct to sutured dural repair in cranial surgery.

The primary endpoint is the proportion of subjects that do not have a CSF leak during surgery and up to the 30-day (-/+ 7) post-operative period.

A subject is declared as a success when the following conditions are met:

- absence of intra-operative CSF leak following final Valsalva maneuver, and
- absence of CSF leak or Pseudomeningocele in the surgical area during the 30-day (-/+ 7) follow-up period.

A confirmed CSF leak or pseudomeningocele is diagnosed by physical examination, diagnostic testing, imaging study or the need for surgical intervention to directly treat a CSF leak during the 30-day (-/+ 7 days) follow-up at the location where randomized treatment was applied.

The secondary endpoints of the study include:

- Incidence of intra-operative CSF leakage following final Valsalva maneuver.
- Incidence of post-operative CSF leakage within 30 (-/+7) days post-operatively.
- Incidence of post-operative CSF leakage within 60 (-/+ 14) days post-operatively.
- Incidence of adverse events.
- Incidence of surgical site infections (SSI) according to NNIS definition and CDC classification within 30 (-/+7) days post-operatively (See Appendix I and II).

## **3. Overview of Study Design**

This is a single-blinded randomized, controlled study evaluating EVICEL® as an adjunct to sutured dural closure compared to DuraSeal™ Dural Sealant System.

Approximately 230 subjects undergoing posterior fossa or supratentorial procedures (craniectomy or craniotomy) will be enrolled in the trial with at least 60 subjects undergoing posterior fossa procedures being randomized.



Upon completion of the sutured dural repair, the closure will be evaluated for intraoperative cerebrospinal fluid (CSF) leakage with a baseline Valsalva maneuver performed to an intra-thoracic pressure between 20-25 cm H<sub>2</sub>O for 5-10 sec. If a spontaneous leak is apparent immediately after dural closure, no Valsalva will be performed.

Subjects who have a CSF leak will be stratified by surgical procedure, posterior fossa or supratentorial approach and then randomized to either EVICEL Fibrin Sealant or DuraSeal™ Dural Sealant System in a 1:1 allocation ratio.

Subjects will be followed post-operatively through discharge and again at 30 (-/+7) days and 60 (-/+14) days post-surgery. For the primary endpoint, the incidence of CSF leaks will be assessed up to the 30 day post-operative follow-up period. The incidence of CSF Leak will also be assessed up to the 60 day post-operative follow-up period. A CSF leak will be reported as detected by any of the following: clinical observation, diagnostic testing, imaging or the need for surgical intervention to directly treat a CSF leak.

## 4. Study Population

### 4.1 General Considerations

The Investigator is expected to invite all patients expected to meet the pre-operative entry criteria to participate in the study.

### 4.2 Inclusion Criteria

#### Pre-Operative

1. Subjects ≥18 years of age undergoing craniotomy/craniectomy for pathological processes in the supratentorial region or posterior fossa (such as benign or malignant tumors, vascular malformation, and Chiari 1 malformations);
2. Subjects or legally authorized representatives must be willing to participate in the study and provide written informed consent.

#### Intra-Operative

1. Surgical wound classification Class I (refer to Appendix II). Superficial penetration of mastoid air cells during partial mastoidectomy is permitted.
2. The cuff of native dura along the craniotomy edge on each side is adequate, based on surgeon's judgment, to facilitate suturing and to allow for sufficient surface area for adherence of the investigational product.
3. Presence of intra-operative cerebrospinal fluid (CSF) leakage following primary dural closure or after Valsalva maneuver

### 4.3 Exclusion Criteria

#### Pre-Operative

1. Subjects with a cranial dural lesion from a recent surgery that still has the potential for CSF leakage.
2. Chemotherapy within 30-days prior to enrollment or scheduled within 7 days following surgery.
3. Radiation therapy to the head within 30-days prior to enrollment or scheduled within 7 days following surgery.
4. A previous craniotomy/craniectomy within 6 months prior to the study surgery.

5. Known hypersensitivity to the components (such as human fibrinogen, arginine hydrochloride, glycine, sodium chloride, sodium citrate, calcium chloride, human thrombin, human albumin, mannitol and sodium acetate) of the investigational product.
6. Subjects with a known allergy to FD&C Blue #1 dye in DuraSeal™.
7. Subjects with an infection present at the surgical site
8. Subjects with an infection indicated by any one of the following: clinical diagnosis of infection, fever, positive urine culture, positive blood culture, positive chest x-ray.
9. Female subjects of childbearing potential with a positive pregnancy test or intent to become pregnant during the clinical study period.
10. Female subjects who are nursing.
11. Exposure to another investigational drug or device clinical trial within 30 days prior to enrollment or anticipated in the 60 day follow-up period.
12. Subjects with severely altered renal or hepatic function, with a compromised immune system or autoimmune disease who can NOT receive DuraSeal™.
13. Subjects with penetrating traumatic injuries to the head with damage to the dura.

### **Intra-Operative**

1. Dural injury during craniotomy/craniectomy that cannot be eliminated by widening the craniotomy/craniectomy to recreate the native dural cuff.
2. Patient has a gap between durotomy edges of greater than 2mm after primary dural closure.
3. Approaches that would not allow sutured dural closure such as trans-sphenoidal or trans-labyrinthine-/petrosal/-mastoid. Superficial penetration of mastoid air cells is allowed.
4. Use of implants made of synthetic materials coming into direct contact with dura (e.g., PTFE patches, shunts, ventricular and subdural drains, existing CSF drains.)
5. Use of other fibrin sealants or PEG-based sealants on the dural closure. Approved fibrin sealants may be used for hemostasis if not in contact with the dura.
6. Hydrocephalus, except occlusive hydrocephalus caused by posterior fossa pathology or incompletely open cerebrospinal fluid pathways to be treated during the planned surgical procedure.
7. Placement of Gliadel Wafers
8. Intersecting durotomy scars in the surgical path from a previous operation that cannot be completely removed by the planned dural resection.
9. Two or more separate cranial dural defects, including defects from ventricular cannulation and ventriculo-peritoneal shunting
10. Subjects with any other intra-operative findings identified by the surgeon that may preclude the conduct of the study procedure.
11. Confined bony structures where nerves are present where neural compression may result due to swelling.

## **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.



## 6. Investigational Product and Comparators

### 6.1 EVICEL® Fibrin Sealant

#### 6.1.1 Formulation

EVICEL® is a human plasma-derived fibrin sealant. EVICEL® consists of two components: a concentrate of Human Fibrinogen (referred to as Biological Component 2; BAC2) and a 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. The applicator device has been designed to ensure even mixing of the two components.

#### Composition of EVICEL®

	Human Fibrinogen	Human Thrombin
Active Ingredient	Concentrate of human fibrinogen (55-85 mg/mL)*	Human thrombin (800-1200 IU/mL)
Other ingredients	Arginine hydrochloride, Glycine, Sodium chloride, Sodium citrate, Calcium	Calcium chloride, Human albumin, mannitol, Sodium acetate, Water for injection (WFI).

	chloride, Water for injection (WFI)	
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\*In EU, specified as 50-90 mg/mL human clottable protein containing mainly fibrinogen and fibronectin.. Each mL of Evicel® contains 11.6-12.9 mg sodium.

### 6.1.2 Labeling and Packaging

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

- Name, address and telephone number of Sponsor
- Protocol number
- EudraCT number
- Vial contents (volume of solution and concentration of active ingredients)
- Storage conditions
- Reference to the Package Leaflet for instructions of preparation and use in the Investigator’s Brochure
- “For Clinical Trial Use Only”
- “Caution: New Drug—Limited by Federal Law to Investigational Use”
- Lot number
- Expiry date

### 6.1.3 Application Device

The application device is commercially available in the US, EU and multiple other countries. It will be used according to its intended instructions and is not considered an investigational product in regions where available. The applicator will be labeled according to local regulatory requirements, and may contain the following information:

- Name, address and telephone number of Ethicon, Inc.
- Protocol number
- “For Clinical Trial Use Only”

### 6.1.4 Accessory Tips

Certain accessory tips are commercially available in several countries. They will be used according to their intended instructions and are not considered as an investigational product in regions where available.

There will be three accessory tips provided for use with the application device:

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

Accessory tips may be used according to surgeon preference. Tips will be used in accordance with their Product Assembly Guide. Depending on its regulatory status and local regulatory requirements, the product will be labeled according to local regulatory requirements, and may contain the following information:

- Name, address and telephone number of Ethicon, Inc.
- Protocol number
- “For Clinical Trial Use Only”

### **6.1.5 Pressure Regulators**

Pressure regulators may be supplied by request. The pressure regulators are commercially available. They will be used according to their intended instructions and are not considered an investigational product.

### **6.1.6 Shipping, Handling, and Storage Conditions**

Distribution of EVICEL® to the clinical sites will be performed by a qualified distribution center with proper inventory and quality control capabilities once all the necessary documentation and approvals are obtained. For distribution in the EU, a qualified person (QP) release will be done prior to distribution.

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, according to the product label.

The application devices, tips, and pressure regulators will be shipped and stored at ambient temperature.

### **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 can be stored at 2-8°C for up to 30 days. Thawed vials must not be re-frozen, and product taken out of the refrigerator should not be returned to the refrigerator.

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/accessory 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® will be thawed and available for administration prior to randomization. EVICEL® will be applied to cover the entire length of the suture line and the adjacent area of the dura to produce a thin, even layer (approx. 1mm thickness). If necessary, a second layer of EVICEL® may be applied. A cure time of 1-2 minutes should be allotted between applications to allow for the clot formation and stabilization. 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 IFU.

## **6.2 DuraSeal® Dural Sealant System**

DuraSeal® will be stored, handled, prepared, and applied according to its label and instructions for use (IFU) or package insert. If necessary, a second layer of DuraSeal™ may be applied.

### **6.3 Investigational Product Dispensation and Accountability**

A dispensing/accountability log will be kept by the designated study personnel containing information on the date of administration, subject ID #, quantity of EVICEL® and DuraSeal™ (if applicable) dispensed, details of remaining product, and subsequent destruction (if applicable). The study monitor will verify these logs during the course of the study. The study product will be stored according to the IB or IFU, respectively, and be kept in a secured area with access restricted. Study product is to be used for study subjects only.

### **6.4 Concomitant Medications**

#### **6.4.1 Documentation of Concomitant Medications**

Indication and start-stop dates of concomitant medications administered from 24 hours prior to surgery up to the 60-day follow-up visit will be recorded. This will include medications that subjects are using chronically.

Anesthetics used for the study surgery and over the counter (OTC) drugs will not be recorded as concomitant medication (with the exception of prophylactic aspirin and those administered to treat adverse events, which should be documented). Concomitant medications used to treat Adverse Events must also be documented, including OTC medications. Doses and routes of administration are not required to be reported.

## **7. Study Evaluations**

### **7.1 Study Procedures**

The schedule of events included in the synopsis summarizes the frequency and timing of the study procedures. All assessments will be performed by the investigator or other study personnel with delegation of authority. Data collected for the subject during the study will be recorded in the subject's medical records, and study worksheets/source documents, as appropriate, and transcribed into the eCRF.

#### **7.1.1 Screening**

Prospective patients will be screened within 30 days prior to surgery. All prospective patients should be listed in the screening and enrollment log. Patients screened but not consented or enrolled should be recorded with a reason for not enrolling. Prior to any study specific procedures, subjects will be appropriately consented and the consenting process documented. Subjects (or legally authorized representative) will be asked to sign an Informed Consent Form. Once the Informed Consent Form is signed, study related information, including information obtained as part of standard clinical practice, may be collected as part of the protocol.

The following tests and activities will be performed or collected at the screening visit. The timing of these activities may occur based on routine hospital practice and may be done up to the day of, but prior to, the study surgery:

- Informed consent process
- Allocation of screening number
- Assessment of pre-operative inclusion and exclusion criteria for subject eligibility
- Documentation of demography (e.g. age, ethnic origin)

- Physical examination, including documentation of relevant medical and surgical history
- Documentation of smoking status, alcohol consumption, history (family and personal) of thromboembolic events

### 7.1.2 Baseline

The following activities/assessments will be done within 24 hours prior to the procedure. The timing of these activities may occur based on routine hospital practice and may overlap with some of the Screening (see Section 7.1.1) activities.

- Review of pre-operative inclusion and exclusion criteria to confirm subject pre-operative eligibility. If the subject is no longer eligible, the reason for screen failure will be documented in the source documentation and the screening log
- Documentation of concomitant medications as outlined in Section 6.4
- Documentation of any changes in medical history since the screening visit (if done on a separate visit from Baseline).
- Laboratory evaluations – samples can be drawn within 7-days prior to the procedure. Labs taken closest to procedure should be used.
  - Electrolyte, blood urea nitrogen (BUN), creatinine
  - Complete blood count (CBC) with differential
  - Liver function tests
  - Serum or urine pregnancy test (if applicable)

### 7.1.3 Surgical Procedure

The investigator will use his or her standard surgical techniques for the surgical procedure. Use of a tissue based patch is permitted for primary sutured dural closure if a watertight seal can be achieved. Upon completion of the sutured dural repair, the closure will be evaluated for intraoperative CSF leakage with a baseline Valsalva maneuver performed to an intra-thoracic pressure between 20-25 cm H<sub>2</sub>O for 5-10 seconds. If a spontaneous leak is apparent immediately after dural closure, no Valsalva maneuver will be performed.

Subjects who have a CSF leak will be stratified by surgical procedure, posterior fossa or supratentorial approach, and then randomized to either EVICEL<sup>®</sup> or DuraSeal<sup>™</sup> in a 1:1 allocation ratio.

EVICEL<sup>®</sup> and DuraSeal<sup>™</sup> will be available in the OR/theatre for administration prior to randomization for each subject.

The following activities/assessments will be done during the surgical procedure:

- Review of inclusion and exclusion criteria to confirm intra-operative eligibility. If the subject is no longer eligible, the reason for screen failure will be documented in the source documentation, the screening log, and the eCRF.
- Documentation of concomitant medications as outlined in Section 6.4
- Hospital admission date (for overall Length of Stay)
- Operating room/theatre details:
  - Enter and exit time
  - Procedure time (first incision to final closure)
- Surgical approach – posterior fossa or supratentorial

- Indication for procedure, (e.g. – A-V malformation, Chiari malformation, aneurysm, epilepsy, tumor, other)
  - If tumor, tumor type details (e.g. acoustic neuroma, frontal, meningioma, parietal, temporal, other)
- Tissue patch details (e.g. autologous/non-autologous), if applicable
- CSF leakage determination (prior to randomization)
- Randomization and treatment details (see below)
  - EVICEL® Treatment (to be captured for each layer applied)
    - Method of application (spray or drip)
    - Accessory tips used (if applicable)
    - Number of layers applied
    - Total volume applied
    - EVICEL® units used
  - DuraSeal™ Treatment
    - Number of layers applied
    - Total volume applied
    - DuraSeal™ units used
- Post-treatment Valsalva maneuver details
  - CSF leakage details (if applicable) – breakthrough CSF leakage, delamination, other
- Rescue treatment (if applicable)
- Adverse events from time of application (through follow-up)

#### **7.1.3.1 Subjects Randomized to EVICEL®**

For subjects randomized to receive EVICEL® Fibrin Sealant (Human), a thin layer will be applied to cover the entire length of the suture line and the adjacent, including all suture holes. If necessary, a second layer of EVICEL® may be applied. A cure time of 1-2 minutes should be allotted between layers to allow for clot formation and stabilization. CSF leakage will be evaluated with the Valsalva maneuver performed to an intra-thoracic pressure between 20-25 cm H<sub>2</sub>O for 5-10 sec.

If a 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 as described above. If watertight closure is achieved for EVICEL® treatment, no further treatment, including the use of onlays, will be allowed.

If watertight closure is not evident after the final Valsalva maneuver, the subject will be deemed a failure and surgeon may revert to his/her standard of care for closure, this can include additional treatment with EVICEL® if clinically appropriate. The use of other fibrin sealants is not permitted.

Subjects randomized to EVICEL® may not have their dura treated with DuraSeal™ Dural Sealant System or any other PEG based or fibrin sealants.

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

#### **7.1.3.2 Subjects Randomized to DuraSeal™**

For subjects randomized to DuraSeal™, the assigned product will be applied to the entire length of the suture line, including all suture holes, according to the manufacturer's instruction for use. CSF leakage will



be evaluated with the Valsalva maneuver performed to an intra-thoracic pressure between 20-25 cm H<sub>2</sub>O for 5-10 seconds.

If a CSF leakage is still apparent, continue treatment with Duraseal™ per manufactures directions. CSF leakage will be re-evaluated with the Valsalva maneuver as described above. If watertight closure is achieved for DuraSeal™ treatment, no further treatment, including the use of onlays, will be allowed.

If watertight closure is not evident after the final Valsalva maneuver, the subject will be deemed a failure and surgeon may revert to his/her standard of care for closure, this can include additional treatment with DuraSeal™, if clinically appropriate. The use of fibrin sealants is not permitted.

Subjects randomized to DuraSeal™ may not have their dura treated with EVICEL® Fibrin Sealant or any other PEG based or fibrin sealants.

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

#### **7.1.4 Post-Surgery through Hospital Discharge**

Concomitant medications and adverse events will be collected throughout the study. The following additional information will also be collected post-surgery through discharge:

- ICU time in days
- Laboratory evaluations – collected within 72 hours prior to discharge (labs taken closest to discharge should be used).
  - Electrolyte, blood urea nitrogen (BUN), creatinine
  - Complete blood count (CBC) with differential
  - Liver function tests
- Physical examination (prior to discharge)
  - Surgical site assessment
  - Wound healing assessment
- Hospital discharge date (for overall Length of Stay)

#### **7.1.5 30-Day Follow-up (-/+7 days)**

The following information will be collected at the clinical follow-up approximately 30 days following surgery:

- Adverse events
- Changes in concomitant medications
- Laboratory evaluations
  - Electrolyte, blood urea nitrogen (BUN), creatinine
  - Complete blood count (CBC) with differential
  - Liver function tests
- Physical examination
  - Surgical site assessment
  - Wound healing assessment

#### **7.1.6 60-Day Follow-up (-/+14 days)**

The 60-Day follow-up visit may take place in-person or over the phone. The following information will be collected at the clinical follow-up approximately 60 days following surgery:

- Adverse events, including occurrence of CSF Leak
- Changes in concomitant medications

## **7.2 Procedures for Handling Biological Samples**

### **7.2.1 Laboratory Tests**

All laboratory investigations will be performed at the 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 must be provided to Sponsor. Laboratory accreditation certificates must be verified.

## **7.3 Premature Withdrawal of Subjects from the Study**

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

- Death;
- Consent withdrawn by the subject;
- Subject refusal to complete study visits and/or procedures;
- Withdrawals due to adverse events
- Lost to follow-up: a certified letter, unless restricted by per local requirements, 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 Data Management and Biostatistics groups of Clinical Development at ETHICON 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 number of randomized subjects required for this trial is 202 subjects (101 per treatment arm) from centers in North America, Europe, and Asia-Pacific. There will be approximately 25 global sites. In order to account for potential missing follow-up information (drop-outs), approximately 230 subjects will be enrolled. At least 60 subjects undergoing posterior fossa procedures will be randomized.

Two hundred and two (202) evaluable subjects (101 per arm) will achieve 90% power to detect a non-inferiority margin difference in group proportions of  $-0.10$ . The proportion of successes in the Control group is 0.95. The proportion of successes in EVICEL<sup>®</sup> group is assumed to be 0.85 under the null hypothesis of inferiority. The power was computed for the case when the actual proportion of successes in the EVICEL<sup>®</sup> group is 0.95. The one-sided significance level of the test is 0.025.

If the lower limit of the one-sided 97.5% confidence interval for  $\Delta$  is greater than -0.10, then it will be concluded that Experimental is considered to be non-inferior to Control.

## 8.2 Data Analysis

The categorical data will be summarized descriptively by frequencies along with associated percentages for each group. The continuous variables will be summarized descriptively by number of subjects, mean, standard deviation, minimum, and maximum for each group. A two-sided 5% significance level will be used for any statistical tests, unless otherwise specified in the protocol.

### 8.2.1 Analysis Sets

There will be three analysis sets defined:

- Evaluable set (or per protocol set) consists of all ITT subjects who have no major protocol violations.
- Intent-to-treat set (ITT or full analysis set) consists of all randomized subjects.
- Safety set consists of all subjects who receive a study treatment.

The primary endpoint analysis will be based on the evaluable set.<sup>16</sup> Surgical procedure (posterior fossa or supratentorial approach) will be utilized as stratification factor in the overall analysis.

Major protocol violations are violations that have an impact on the primary endpoint, or that have an impact on the randomization assignment. These will be determined prior to database lock.

## 8.3 Effectiveness

### 8.3.1 Effectiveness Variables

The primary endpoint is the proportion of subjects that do not have a CSF leak during surgery and up to the 30-day (-/+7) post-operative period. A subject is declared as a success when the following conditions are met:

- absence of intra-operative CSF leak following Valsalva maneuver, and
- absence of CSF leak or pseudomeningocele in the surgical area during the 30-day follow-up period.

The primary effectiveness parameter will be analyzed using the ITT and Per-Protocol analysis sets. The Per-Protocol analysis will be considered primary effectiveness analysis.

There are no secondary effectiveness endpoints for this study.

### 8.3.2 Methods of Analysis

The statistical hypothesis for testing the treatment difference is presented as follows:

- $H_0: \Delta \leq -0.10$  tested against the alternative hypothesis
- $H_a: \Delta > -0.10$ .

where:

- $\Delta$  is the difference between the success rates of Experimental and Control (Experimental minus Control)

- -0.10 is the non-inferiority difference
- The assumed proportion of successes for Control is 0.95.

$P_C$  is the proportion of success in DuraSeal™ Control subjects and  $P_E$  is the proportion of success in EVICEL® subjects.

Two hundred and two (202) evaluable subjects (101 per arm) will achieve 90% power to detect a non-inferiority margin difference in group proportions of -0.10. The proportion of successes in the Control group is 0.95. The proportion of successes in EVICEL® group is assumed to be 0.85 under the null hypothesis of inferiority. The power was computed for the case when the actual proportion of successes in the EVICEL® group is 0.95.<sup>6,14</sup> The one-sided significance level of the test is 0.025.

If the lower limit of the one-sided 97.5% confidence interval for  $\Delta$  is greater than -0.10, then it will be concluded that Experimental is considered to be non-inferior to Control.

For the primary endpoint, the comparability between the surgical procedure (posterior fossa or supratentorial approach) subgroups will be evaluated using a logistic regression analysis, with success/failure for primary endpoint as dependent variable and with surgical procedure, treatment group and interaction between surgical procedure and treatment group as independent variables included in the model. The interaction term will be considered significant at 0.15 significance level in the logistic regression. In addition, the primary endpoint will be compared between treatment groups using a CMH Chi-square test adjusting for the surgical procedure.

## 8.4 Safety

### 8.4.1 Safety Variables/Criteria

The following will be summarized using the Safety Set:

- Incidence of adverse events
- Laboratory tests
- Incidence of surgical site infections (SSI) according to NNIS definition and CDC classification within 30 days (-/+ 7) post-operatively.
- Incidence of Intra-operative CSF leakage following final Valsalva maneuver.
- Incidence of post-operative CSF leakage within 30 days (-/+ 7) post-operatively.
- Incidence of post-operative CSF leakage within 60 (-/+ 14) days post-operatively.

### 8.4.2 Methods of Analysis

Adverse events will be summarized descriptively using Medical Dictionary for Regulatory Activities (MedDRA) terminology. Laboratory evaluations (baseline and post-surgery samples) will be summarized in SI units. No inferential statistical analysis will be performed for the safety endpoints.

## 8.5 Handling of Missing Data

The primary analysis will be the Per-Protocol analysis. It is not anticipated that there will be any data missing for treated subjects for the primary endpoint, but if there is, sensitivity analyses will be performed considering missing data as failures, successes, and as worst-case, with missing data for the EVICEL® group considered as failures and missing data for the DuraSeal™ group considered as successes.

## 8.6 Health Economics

Health Economic data will be collected in this evaluation including products used for this rescue treatment (if applicable), Length of Stay, Days in ICU, and OR times. These data points will be analyzed descriptively.

## 9. Safety

### 9.1 Adverse Event

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** (AE, 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 judgment about causality.

### 9.2 Serious Adverse Event

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

- Results in death;
- Is considered to be life-threatening;
- Requires in-patient 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 congenital anomaly or birth defect;
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization. The event may be considered serious when, based on appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

**Life threatening** refers to an event 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. All other events that are considered medically serious by the investigator should also be reported.

Hospitalization is defined as the patient being admitted and hospitalized for more than 24 hours. 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 SAE, except hospitalizations for the following:

- Social reasons in absence of an AE;
- Surgery or procedure planned before entry into the study (must be documented in the case report form)
- Emergency room visits unless the subject is admitted.

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

**Unexpected adverse event** or **unexpected suspected adverse reaction**. An AE or suspected adverse reaction is considered 'unexpected' if it is not listed in the investigator brochure or in the product labeling (USPI, SmPC etc.) or is not listed at the specificity or severity that has been observed. 'Unexpected' also refers to events that are mentioned as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

**Suspected, unexpected, serious adverse drug reactions (SUSAR)** are serious adverse drug reactions that are suspected of being related to the drug and are unexpected.

### 9.3 Relationship

The relationship of the product to an AE must be determined using the following classification:

- **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.

The relationship of the surgical procedure to an AE must be determined using the following classification:

- **None:** No relationship to the surgical procedure.
- **Possible:** Reasonable possibility that the event was caused by the surgical procedure.
- **Related:** The event was certainly or probably caused by the surgical procedure.

### 9.4 Severity

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

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

### 9.5 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 start of randomization during the procedure, through the hospital admission, and until completion of the 60-day follow-up visit.

All AEs will be documented in the subject's source document (e.g. medical records) and electronic case report forms. All AEs will be followed until completion of the 60-day follow-up visit or until a stable resolution, whichever is sooner.

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/ IB or as a result of user error. The Investigator must contact the Sponsor should this occur.

### 9.6 Adverse Event Reporting

It is a requirement that the Investigator promptly report all SAEs (irrespective of relationship to the study product) 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:

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

The Sponsor will report any SUSARs to the regulatory authorities and IRBs/Ethics Committees within the required timeframes of 7 calendar days for fatal or life-threatening SUSARs and 15 calendar days for all other SUSARs.

### 9.7 Device Complaint Handling

If a device failure occurs with the EVICEL® applicator device, accessory tips or pressure regulator, a Device Complaint Form must be completed and [REDACTED]. Included are those complaints related to the applicator devices, accessory tips or pressure regulator 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.

Complaints related to DuraSeal™ should be reported to the manufacturer according to the Package Insert.

## 10. Regulatory Obligations

### 10.1 Informed Consent

Prior to participation, Informed Consent will be appropriately obtained and documented. The study procedures and any known or likely risks will be explained to the subjects or subject’s legal representative, by the Investigator or individuals delegated the authority by the Principal Investigator.

An IRB/EC approved Informed Consent Form (ICF) will be provided containing all the required information per ICH guidelines and applicable regional requirements. Any questions will be answered and the subject will then be given sufficient time to consider their participation in the study before signing a consent form. Subjects should receive a signed and dated copy of the ICF.

The Investigator (or designee) will explain that the subjects 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 will be informed that his/her 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 subject ID number will identify them.

## **10.2 Institutional Review Boards/Ethics Committees**

The Investigator must submit the protocol, protocol amendments, informed consent forms, any subject information sheets, advertising materials and other applicable documents to the appropriate Institutional Review Board (IRB) or Ethics Committee (EC) according to local requirements. Approval from the IRB/EC must be obtained prior to starting any study-related procedures. Investigational product will not be shipped to a site until written IRB/EC authorization has been received by the sponsor or its representative.

## **10.3 Data Management**

### **10.3.1 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 Medidata 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 subject 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 Medidata® Rave 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.

### **10.3.2 Data Collection**

The Investigator must maintain required records on all study subjects. Data for this study will be recorded in the subjects 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 with 21 CFR Part 312 and applicable regional requirements. All data on the eCRFs should be recorded from appropriate source documentation.

Each EDC eCRF will be completed by the Principal Investigator (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. A unique ID number will be visible on each eCRF. 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.

### **10.3.3 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 Medidata® Rave.



### **10.3.4 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 # provides the link between named subject source records in the subject file and anonymous eCRF data provided to SPONSOR.

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. If regional regulations differ, the investigator must retain study related documents by whichever is longer. Study documents should not be destroyed without prior written agreement between the Investigator and SPONSOR. The sponsor must be notified if the Investigator wishes to assign the study records to another party, or move them to another location.

## **10.4 Study Monitoring and Auditing**

This study will be monitored at all stages of its development by the clinical research personnel employed by the Sponsor or its representative. Monitoring will include site visits, review of eCRF data, and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with guidelines of Good Clinical Practice. On-site review of eCRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject. Note that a variety of original documents, data, and records will be considered as source documents in this trial.

The study may be subject to audit by the sponsor or by regulatory authorities. If such an audit occurs, the Investigator must agree to allow access to required subject records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation.

## **10.5 Sponsor Obligations**

### **10.5.1 Monitoring**

The monitor or designee will contact and visit the Investigator regularly and must be allowed to monitor the trial. The monitor will visit as soon as possible following enrollment for the first subject and at regular intervals during the study (approximately every four to six weeks) as deemed necessary. It will be monitor's responsibility to inspect study records at regular intervals throughout the study, to verify adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries, and ensure patient protection.

### **10.5.2 Regulatory Requirements**

This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

### **10.5.3 Liability and Insurance Conditions**

In case of any damage or injury occurring to a subject in association with the trial medication, Sponsor has product liability insurance. A copy of this policy is on file at the Sponsor.

## **11. Investigator Obligations**

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

### **11.1 Financial Disclosure**

The investigator is responsible for updating the Sponsor if there are any changes that would affect their Financial Disclosure during the conduct of the study.

### **11.2 Audit and Inspection**

The Investigator (and head of institution, if required by regional regulations) will make source data and documents for this study available to an appropriately qualified quality assurance auditor mandated by Sponsor or to regulatory authority inspectors, after appropriate notification.

### **11.3 Confidentiality of Subject Records**

The Investigator will ensure that the subjects' anonymity will be maintained. On eCRFs or other study documents submitted to Sponsor, 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 subject ID number. Documents not for submission to Sponsor, i.e. Subject Identification Log and original subjects' informed consent forms, will be maintained in the Investigator Site File.

### **11.4 Record Retention**

The Investigator must retain all study related documentation until at least 2-years after the final indication is approved, or at least 2-years have elapsed since the formal discontinuation of the clinical study. If regional regulations differ, the investigator must retain study related documents by whichever is longer. Study documents should not be destroyed without prior written agreement between the Investigator and Sponsor. The Sponsor must be notified if the Investigator wished to assign the study records to another party or move the records to another location. The Investigator will take measure to prevent accidental or premature destruction of these documents.

## **12. Changes to the Protocol**

### **12.1 Protocol Amendments**

All protocol amendments are required to be submitted for information/consideration to the regulatory authorities, IRBs/ECs. Documentation of approval is required before implementation of amendments.

### **12.2 Clinical Trial Termination**

Both the Investigator and Sponsor 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, Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests and safety.

### **12.3 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 continued development of the EVICEL® Fibrin Sealant 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, Inc. 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 Johnson & Johnson (J&J), Ethicon, ETHICON™ Biosurgery, Fibrin Sealant (EVICEL®), EVICEL® Fibrin Sealant, or any of its employees in any publicity, news release, or other public announcement, written or oral, whether to the public, press, or otherwise, related to this protocol, to any amendment hereto, or to the performance hereunder, without the prior consent of Ethicon, Inc.

### 13. Contact Details

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## Appendix I: 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 II: 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.