Clinical trial results:
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

Summary

EudraCT number	2014-003954-15
Trial protocol	GB BE
Global end of trial date	12 October 2017

Results information

Result version number	v1 (current)
This version publication date	26 October 2018
First version publication date	26 October 2018

Trial information

Trial identification

Sponsor protocol code	BIOS-14-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02457546
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ETHICON Inc
Sponsor organisation address	Route 22 West, Somerville, United States, 08876
Public contact	Heather Paleczny, Principal Research Scientist, Ethicon, Inc., 1 9082182081, hpaleczn@its.jnj.com
Scientific contact	Dr Richard Kocharian, Sr Medical Director , Ethicon, Inc., 1 9082182031, rkochar1@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 October 2017
Global end of trial reached?	Yes
Global end of trial date	12 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The protocol and consent form were provided to the appropriate ethics committee for review and approval.

Background therapy:

Not applicable.

Evidence for comparator:

The comparator for this trial was DuraSeal™ Dural Sealant System. The efficacy and safety of DuraSeal™ Dural Sealant System as an adjunct to sutured dural repair to obtain watertight closure during cranial surgery was demonstrated in a prospective multicenter study of 111 patients. DuraSeal™ was 100% effective in obtaining watertight closure. Efficacy was also demonstrated in another multicenter single-blind prospective randomized trial in 237 patients exhibiting non-watertight dural closure during cranial surgery which showed the safety profile of DuraSeal™ to be similar to other commonly used dural closure techniques.

DuraSeal™ Dural Sealant System is a commercially available synthetic sealant intended for use as an adjunct to sutured dural repair during cranial surgery to provide watertight closure. The product is a synthetic absorbable sealant composed of a polyethylene glycol (PEG) ester solution and a rilysine amine solution.

DuraSeal™ Dural Sealant is approved in the US (since 2005), in EU (since 2003) and in numerous countries world-wide.

Actual start date of recruitment	01 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 71
Country: Number of subjects enrolled	Belgium: 44
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	New Zealand: 23
Country: Number of subjects enrolled	United States: 75
Worldwide total number of subjects	234
EEA total number of subjects	115

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	171
From 65 to 84 years	60
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The first patient was recruited on 7th July 2015 and the last patient, last visit was 12th October 2017.

Pre-assignment

Screening details:

Prospective patients were screened within 30 days prior to surgery. Prior to any study specific procedures, subjects were fully informed of all aspects of the study, and the consenting process was documented.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

This was a single-blinded study where the subject was blinded to treatment. Subjects remained blinded throughout the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	EVICEL® Fibrin Sealant (Human)

Arm description:

EVICEL® is a human plasma-derived fibrin sealant consisting of two components: Human Fibrinogen (also named Biologically Active Component 2 (BAC2), and Human Thrombin containing Calcium (EVICEL® Fibrin Sealant (Human).

Arm type	Experimental
Investigational medicinal product name	DuraSeal™ Dural Sealant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sealant
Routes of administration	Topical use

Dosage and administration details:

For subjects randomized to DuraSeal™, the assigned product was applied to the entire length of the suture line, including all suture holes, according to the manufacturer's instruction for use. No patient received more than 10ml.

Investigational medicinal product name	EVICEL® Fibrin Sealant (Human)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sealant
Routes of administration	Topical use

Dosage and administration details:

For each subject, at least one kit of EVICEL® (2ml each of BAC2 and Thrombin [total 4ml]) was pre-prepared in the applicator kit prior to randomization. EVICEL® was to be applied to the surgical site by either spraying or dripping onto the dural suture line. If necessary, a second layer of EVICEL® could be applied. No patient received more than 2 kits (8ml)

Arm title	DuraSeal™ Dural Sealant

Arm description:

DuraSeal™ Dural Sealant System is a synthetic absorbable sealant composed of a polyethylene glycol (PEG) ester solution and a rilysine amine solution used as an adjunct to sutured dural repair during cranial surgery to provide watertight closure.

Arm type	Synthetic Sealant
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	EVICEL® Fibrin Sealant (Human)	DuraSeal™ Dural Sealant
Started	114	120
Completed	105	116
Not completed	9	4
Adverse event, serious fatal	3	2
Physician decision	1	-
Subject refusal to attend further visits	1	1
Lost to follow-up	4	1

Baseline characteristics

Reporting groups	
Reporting group title	EVICEL® Fibrin Sealant (Human)
Reporting group description:	
EVICEL® is a human plasma-derived fibrin sealant consisting of two components: Human Fibrinogen (also named Biologically Active Component 2 (BAC2), and Human Thrombin containing Calcium (EVICEL® Fibrin Sealant (Human).	
Reporting group title	DuraSeal™ Dural Sealant
Reporting group description:	
DuraSeal™ Dural Sealant System is a synthetic absorbable sealant composed of a polyethylene glycol (PEG) ester solution and a rilysine amine solution used as an adjunct to sutured dural repair during cranial surgery to provide watertight closure.	

Reporting group values	EVICEL® Fibrin Sealant (Human)	DuraSeal™ Dural Sealant	Total
Number of subjects	114	120	234
Age categorical Units: Subjects			
Adults (18-64 years)	86	85	171
From 65-84 years	27	33	60
85 years and over	1	2	3
Gender categorical Units: Subjects			
Female	59	59	118
Male	55	61	116

Subject analysis sets	
Subject analysis set title	Intent to Treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Consists of all randomized subjects	
Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
Consists of all ITT subjects who have data available for primary effectiveness endpoint and have no major protocol deviations	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who receive a study treatment.	

Reporting group values	Intent to Treat	Per Protocol	Safety Set
Number of subjects	234	208	234
Age categorical Units: Subjects			
Adults (18-64 years)	171	153	171
From 65-84 years	60	53	60
85 years and over	3	2	3

Gender categorical Units: Subjects			
Female	118	102	118
Male	116	106	116

End points

End points reporting groups

Reporting group title	EVICEL® Fibrin Sealant (Human)
Reporting group description:	
EVICEL® is a human plasma-derived fibrin sealant consisting of two components: Human Fibrinogen (also named Biologically Active Component 2 (BAC2), and Human Thrombin containing Calcium (EVICEL® Fibrin Sealant (Human).	
Reporting group title	DuraSeal™ Dural Sealant
Reporting group description:	
DuraSeal™ Dural Sealant System is a synthetic absorbable sealant composed of a polyethylene glycol (PEG) ester solution and a rilysine amine solution used as an adjunct to sutured dural repair during cranial surgery to provide watertight closure.	
Subject analysis set title	Intent to Treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Consists of all randomized subjects	
Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
Consists of all ITT subjects who have data available for primary effectiveness endpoint and have no major protocol deviations	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who receive a study treatment.	

Primary: Primary Endpoint

End point title	Primary Endpoint
End point description:	
The primary endpoint was the proportion of subjects that did not have a CSF leak during surgery and up to the 30 (-/+7)-day post-operative period.	
End point type	Primary
End point timeframe:	
30 days +/- 7 days	

End point values	EVICEL® Fibrin Sealant (Human)	DuraSeal™ Dural Sealant	Per Protocol	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	102[1]	106[2]	208	
Units: Number of successes				
Number of successes	95	92	187	

Notes:

[1] - Per protocol

[2] - Per protocol

Statistical analyses

Statistical analysis title	Primary Endpoint

Statistical analysis description:

The statistical hypothesis for testing the treatment difference is presented as follows:
H0: $\Delta \leq 0.10$ tested against the alternative hypothesis
Ha: $\Delta > 0.10$.
where:
Δ is the difference between the success rates of Experimental and Control (Experimental minus Control)
0.10 is the noninferiority difference
The assumed proportion of successes for Control is 0.95

Comparison groups	EVICEL® Fibrin Sealant (Human) v DuraSeal™ Dural Sealant
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Method	Wald CI
Parameter estimate	non-inferiority
Point estimate	0.063
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-0.018
Variability estimate	Standard deviation

Notes:

[3] - The study is one-sided, non-inferiority, using the 97.5% level (one sided significance level of 0.025). The primary endpoint is CSF leak to 30 days post-surgery.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were recorded as they were reported, whether spontaneously, volunteered, or in response to questioning about well-being. AEs were collected from the start of randomization during the procedure, through the hospital admission, and until completion

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	EVICEL® Fibrin Sealant

Reporting group description:

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.

Reporting group title	DuraSeal™ Dural Sealant

Reporting group description:

DuraSeal™ Dural Sealant is a synthetic absorbable sealant composed of a polyethylene glycol (PEG) ester solution and a rilysine amine solution.

Serious adverse events	EVICEL® Fibrin Sealant	DuraSeal™ Dural Sealant	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 114 (28.07%)	37 / 120 (30.83%)	
number of deaths (all causes)	3	3	
number of deaths resulting from adverse events	3	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
recurrence of glioblastoma			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
residual right front brain tumor			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
worsening of glioblastoma			
subjects affected / exposed	1 / 114 (0.88%)	3 / 120 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	

carcinomatosis meningitis			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
glioblastoma disease progression			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
progression of non-small cell lung cancer			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
progression of melanoma brain metastasis			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
recurrence of fronto-parietal tumor			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
residual brain tumor			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
malignant melanoma disease progression			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	0 / 114 (0.00%)	2 / 120 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subgaleal haematoma			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
uncontrolled high blood pressure			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
shortness of breath			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
upper airway edema			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
bilateral pulmonary embolism			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
altered mental status			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

mental status decline			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
raised white cell count			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Pseudomeningocele			
subjects affected / exposed	2 / 114 (1.75%)	9 / 120 (7.50%)	
occurrences causally related to treatment / all	2 / 2	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
right subdural haemorrhage			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
intra-parenchimal haemmorrhage			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
left subdural haemorrhage			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
subcutaneous fluid collection			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
chronic subdural hematoma			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 114 (0.88%)	5 / 120 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
atypical syncopal episode			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CSF leakage			
subjects affected / exposed	3 / 114 (2.63%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
metastatic melanoma L5 compression			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
middle cerebral artery infarct			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
severe headache			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
worsening of dysphasia post operatively			

subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar haemorrhage			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
headache post-op			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhagic stroke due to ICH/IVH			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subdural hygroma			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral oedema			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
grand mal seizures			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MCA divisional infarct			

subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
worsening headache			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
stroke			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
blind in left eye			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
esophageal bleed			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

small bowel obstruction			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
perforated sigmoid colon			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
kidney stone			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
epidural empyema			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hospital acquired pneumonia			
subjects affected / exposed	1 / 114 (0.88%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			

subjects affected / exposed	1 / 114 (0.88%)	2 / 120 (1.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
post craniotomy deep surgical site infection			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
propionibacterium acnes extradural surgical site infection			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
superficial wound infection			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
post operative wound infection			
subjects affected / exposed	0 / 114 (0.00%)	2 / 120 (1.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
deep wound infection			
subjects affected / exposed	1 / 114 (0.88%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
health care associated pneumonia			

subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sepsis unknown origin			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
surgical wound infection [mrsa]			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
multilobar pneumonia			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Lactic acidosis			
subjects affected / exposed	0 / 114 (0.00%)	1 / 120 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 114 (0.88%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	EVICEL® Fibrin Sealant	DuraSeal™ Dural Sealant	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 114 (90.35%)	109 / 120 (90.83%)	
Injury, poisoning and procedural complications			
incisional site pain			
subjects affected / exposed	11 / 114 (9.65%)	12 / 120 (10.00%)	
occurrences (all)	13	12	

Procedural pain			
subjects affected / exposed	19 / 114 (16.67%)	19 / 120 (15.83%)	
occurrences (all)	19	20	
Wound secretion			
subjects affected / exposed	6 / 114 (5.26%)	8 / 120 (6.67%)	
occurrences (all)	9	9	
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 114 (9.65%)	12 / 120 (10.00%)	
occurrences (all)	12	12	
Hypotension			
subjects affected / exposed	6 / 114 (5.26%)	8 / 120 (6.67%)	
occurrences (all)	6	9	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	5 / 114 (4.39%)	6 / 120 (5.00%)	
occurrences (all)	5	6	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 114 (4.39%)	10 / 120 (8.33%)	
occurrences (all)	5	10	
Hemiparesis			
subjects affected / exposed	7 / 114 (6.14%)	3 / 120 (2.50%)	
occurrences (all)	7	3	
Headache			
subjects affected / exposed	35 / 114 (30.70%)	53 / 120 (44.17%)	
occurrences (all)	45	62	
General disorders and administration site conditions			
chest pain			
subjects affected / exposed	5 / 114 (4.39%)	6 / 120 (5.00%)	
occurrences (all)	5	6	
Fatigue			
subjects affected / exposed	4 / 114 (3.51%)	6 / 120 (5.00%)	
occurrences (all)	4	6	
Pyrexia			

subjects affected / exposed	3 / 114 (2.63%)	10 / 120 (8.33%)	
occurrences (all)	3	11	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	32 / 114 (28.07%)	29 / 120 (24.17%)	
occurrences (all)	35	30	
Vomiting			
subjects affected / exposed	19 / 114 (16.67%)	14 / 120 (11.67%)	
occurrences (all)	20	15	
Constipation			
subjects affected / exposed	32 / 114 (28.07%)	29 / 120 (24.17%)	
occurrences (all)	35	31	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 114 (0.00%)	7 / 120 (5.83%)	
occurrences (all)	0	7	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	3 / 114 (2.63%)	7 / 120 (5.83%)	
occurrences (all)	3	7	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	6 / 114 (5.26%)	1 / 120 (0.83%)	
occurrences (all)	7	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2015	Up-dated to clarify inclusion/exclusion criteria. Craniotomy edge up-dated to be based on surgeon's standard practice. Exclusion of radio therapy within 2 years of procedure was removed. Clarified signs/symptoms of systemic infection. Additional text add to provide clarity on subjects with hydrocephalus. Occlusive hydrocephalus patients were originally excluded. Up-dated to "Hydrocephalus, except occlusive hydrocephalus caused by posterior fossa pathology or incompletely open cerebrospinal fluid pathways, to be treated during surgical procedure. Cuff of native dura along craniotomy edge was defined as >=10mm wide was up-dated to remove width and be based on surgeon's standard practice. Typographical error regarding tip size. Corrected from 6cm to 4cm. Laboratory/Coagulation/Pregnancy evaluations moved from screening to baseline. Up-dated to clarify must be conducted within 24 hours of surgery. Up-date to contact list
17 November 2015	Introduction Clarify that the referenced clinical studies were multicentre, prospective, controlled, randomized Clarify that the potential neurotoxic effects have been demonstrated in experimental in-vivo studies for QUIXIL/CROSSEAL. Information from clinical studies indicated no particular safety concerns Reference to "Dural repair site" added to paragraph for clarity Introduction stated "for use in tissue adhesion/sealing and suture support in neurosurgery". The word "adhesion" was removed as this is a sealing study only Procedure Section Clarify EVICEL® application + to be more consistent with standard surgical practice. Removal of text defining 5mm margin was required. Cure time between layers was up-dated from allowing polymerization to "allow for the EVICEL® clot formation + stabilization" Clarify that patients treated with EVICEL® could not receive DuraSeal™ or any other PEG based or fibrin sealants Add "cranial" before dural lesion for clarity Refer to OR/theatre rather sterile field Confirm that DuraSeal™ must be removed from OR/theatre (originally referred to as sterile field) Incl/Excl No chemotherapy or radiation therapy within 30 days prior to enrollment. Time frame added to be more consistent with surgical practice Traumatic head injuries up-dated to include “penetrating” traumatic injuries to the head with damage to the dura Included "cranial". Two or more separate "cranial" dural defects Other Up-dated contact list(s) Typographical up-date. Added word "maneuver" after valsalva Reference to unopened vials being stored at 25 days in EU/ANZ removed Lab evaluations up-dated to be within 7 days of procedure Removal of coagulation sample Data analysis up-dated to include two-sided 5% significance Definition of inpatient hospitalization up-dated Source for assessing SUSARs up-dated to include product labelling

16 May 2016	Incl/Excl Up-dated to state that approved fibrin sealants may be used for haemostasis if not in contact with dura Two or more separate cranial dural defects up-dated to include the text "including defects from ventricular cannulation and ventriculo-peritoneal shunting" Procedure Up-dated to confirm that the use of onlays is not allowed if watertight closure is achieved for EVICEL®/DuraSeal™ Up-dated to confirm DuraSeal™ patients should not receive EVICEL® in the study treatment area. Other Number of sites increased from 25 to 30 Up-dates to contact list

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Limitations : None Caveats : As lower limit of two-sided 95% CI for difference in proportions of success (Evicel® minus Duraseal™) (-0.018) is greater than non-inferiority margin (-0.10), the non-inferiority of Evicel® to Duraseal™ is demonstrated.

Notes: