Clinical trial results:
A Randomized, Controlled Study to Evaluate the Safety and Effectiveness of Evicel as an Adjunct to Sutured Dural Repair

Summary

EudraCT number	2009-016501-41
Trial protocol	DE BE NL FI GB
Global end of trial date	25 October 2011

Results information

Result version number	v1 (current)
This version publication date	05 August 2016
First version publication date	05 August 2016

Trial information

Trial identification

Sponsor protocol code	400-09-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01174992
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ethicon Inc., a Johnson & Johnson Co.
Sponsor organisation address	Route 22 West , Somerville, United States,
Public contact	Jonathan Batiller, Ethicon Inc., a Johnson & Johnson Co., 001 9082182492, JBatill2@its.jnj.com
Scientific contact	Jonathan Batiller, Ethicon Inc., a Johnson & Johnson Co., 001 9082182492, JBatill2@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	07 December 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 October 2011
Global end of trial reached?	Yes
Global end of trial date	25 October 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to evaluate the safety and efficacy of Evicel for use as an adjunct to dura sutures in elective cranial surgery to provide intraoperative watertight closure.

Protection of trial subjects:

The protocol and consent form were provided to the appropriate Ethics Committee for approval.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 2010
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	Netherlands: 4
Country: Number of subjects enrolled	United Kingdom: 48
Country: Number of subjects enrolled	Belgium: 43
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Australia: 3
Worldwide total number of subjects	139
EEA total number of subjects	136

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)	104
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first subject was consented on the 30 June 2010 and the last subject completed 25-Oct-2011.

Pre-assignment

Screening details:

Prospective subjects were screened within 21 days prior to surgery. Prior to any study related procedures, subjects were fully informed of all aspects of the study and asked to sign a consent form.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	EVICEL

Arm description:

EVICEL is a human plasma-derived fibrin sealant, consisting of two components: Biological Active Component 2 (BAC2), comprising human fibrinogen, and a stabilized solution of Human Thrombin, which incorporates Calcium.

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

Dosage and administration details:

For each subject, 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.

Arm title	Sutures

Arm description:

Sutures

Arm type	Sutures

No investigational medicinal product assigned in this arm

Number of subjects in period 1	EVICEL	Sutures
Started	89	50
Completed	79	47
Not completed	10	3
Consent withdrawn by subject	-	1
Pt refused to complete visit	3	1

No 30 day visit scheduled	2	-
Start of radiation therapy	1	-
Lost to follow-up	4	1

Baseline characteristics

Reporting groups	
Reporting group title	EVICEL
Reporting group description:	
EVICEL is a human plasma-derived fibrin sealant, consisting of two components: Biological Active Component 2 (BAC2), comprising human fibrinogen, and a stabilized solution of Human Thrombin, which incorporates Calcium.	
Reporting group title	Sutures
Reporting group description:	
Sutures	

Reporting group values	EVICEL	Sutures	Total
Number of subjects	89	50	139
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	56	59.5	
full range (min-max)	20 to 78	29 to 75	-
Gender categorical			
Units: Subjects			
Female	45	27	72
Male	44	23	67

Subject analysis sets	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis set	

Reporting group values	FAS		
Number of subjects	139		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			

Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	56		
full range (min-max)	20 to 78		
Gender categorical Units: Subjects			
Female	72		
Male	67		

End points

End points reporting groups

Reporting group title	EVICEL
Reporting group description:	
EVICEL is a human plasma-derived fibrin sealant, consisting of two components: Biological Active Component 2 (BAC2), comprising human fibrinogen, and a stabilized solution of Human Thrombin, which incorporates Calcium.	
Reporting group title	Sutures
Reporting group description:	
Sutures	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis set	

Primary: Proportion of success (intraoperative watertight closure) in the treatment of intraoperative CSF leakage defined as no CSF leakage from dural repair intraoperatively, during Valsalva maneuver 20-25cm H20 for 5-10 seconds

End point title	Proportion of success (intraoperative watertight closure) in the treatment of intraoperative CSF leakage defined as no CSF leakage from dural repair intraoperatively, during Valsalva maneuver 20-25cm H20 for 5-10 seconds
End point description:	
Proportion of success (intraoperative watertight closure) in the treatment of intraoperative CSF leakage defined as no CSF leakage from dural repair intraoperatively, during Valsalva maneuver 20-25cm H20 for 5-10 seconds	
End point type	Primary
End point timeframe:	
Intraoperative	

End point values	EVICEL	Sutures		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	50		
Units: Number of successes	82	19		

Statistical analyses

Statistical analysis title	Primary endpoint
Comparison groups	Sutures v EVICEL
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Chi-squared

Notes:
[1] - P value of < 0.001 was also found during analysis using Fisher's exact test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE's were collected from the start of randomization, throughout the hospital admission and until completion of the 30 day follow up visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	EVICEL

Reporting group description:

EVICEL is a human plasma-derived fibrin sealant, consisting of two components: Biological Active Component 2 (BAC2), comprising human fibrinogen, and a stabilized solution of Human Thrombin, which incorporates Calcium.

Reporting group title	Sutures

Reporting group description:

Sutures

Serious adverse events	EVICEL	Sutures	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 89 (11.24%)	4 / 50 (8.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastasis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 50 (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			
Subcutaneous haematoma			
subjects affected / exposed	0 / 89 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			

subjects affected / exposed	1 / 89 (1.12%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fluid rhinorrhoea			
subjects affected / exposed	1 / 89 (1.12%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial palsy			
subjects affected / exposed	1 / 89 (1.12%)	0 / 50 (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	0 / 89 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 89 (1.12%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural hygroma			
subjects affected / exposed	1 / 89 (1.12%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	1 / 89 (1.12%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 89 (1.12%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Dysphagia			
subjects affected / exposed	1 / 89 (1.12%)	0 / 50 (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			
Pulmonary embolism			
subjects affected / exposed	0 / 89 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 89 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Meningitis			
subjects affected / exposed	1 / 89 (1.12%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 89 (1.12%)	0 / 50 (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	Sutures	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 89 (64.04%)	31 / 50 (62.00%)	

Vascular disorders Hypertension subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all)	 12 / 89 (13.48%) 13 6 / 89 (6.74%) 6	 8 / 50 (16.00%) 8 1 / 50 (2.00%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 17 / 89 (19.10%) 20	 6 / 50 (12.00%) 6	
General disorders and administration site conditions Swelling subjects affected / exposed occurrences (all)	 4 / 89 (4.49%) 5	 5 / 50 (10.00%) 5	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 9 / 89 (10.11%) 10 9 / 89 (10.11%) 10	 3 / 50 (6.00%) 3 1 / 50 (2.00%) 1	
Respiratory, thoracic and mediastinal disorders Respiratory failure subjects affected / exposed occurrences (all)	 4 / 89 (4.49%) 4	 4 / 50 (8.00%) 4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2010	A number of updates were made to clarify: Pressure to be used for the Valsalva maneuver Exclusion of pediatric patients Use of non-autologous tissue based patches
01 October 2010	A number of updates to clarify: Use of Fibrin sealant as a rescue treatment The use of adjunct for durability of closure for the control group Various inclusion/exclusion criteria It also covered increasing the number of sites.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported