Clinical trial results:
A Single Blind, Randomized, Controlled Study to Evaluate the Safety and Effectiveness of EVICEL® as an Adjunct to Gastrointestinal Anastomosis Techniques

Summary

EudraCT number	2011-005479-17
Trial protocol	GB BE
Global end of trial date	06 January 2014

Results information

Result version number	v1 (current)
This version publication date	16 July 2016
First version publication date	16 July 2016

Trial information

Trial identification

Sponsor protocol code	400-11-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01589822
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	Senior Clinical Director, Ethicon Inc., a Johnson & Johnson Co., 1 9082182492, jbatill2@its.jnj.com
Scientific contact	Senior Clinical Director, Ethicon Inc., a Johnson & Johnson Co., 1 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	06 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 January 2014
Global end of trial reached?	Yes
Global end of trial date	06 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and effectiveness of EVICEL® Fibrin Sealant (Human) for use as an adjunct to stapled anastomosis after lower anterior resection (LAR).

This will be done by assessing the absence of clinical anastomotic leak (success) within 40 days post operatively.

Clinical anastomotic leak is defined as signs and symptoms that are confirmed by one or more of the following methods:
• Confirmation on imaging;
• Visual confirmation (eg., reoperation/drain output).

Protection of trial subjects:

The protocol and consent form were provided to the appropriate Ethics Committee for approval.In addition, an independent Data Monitoring Committee was established and had responsibility for evaluating the progress of the trial and assessing patient safety and data quality.

Background therapy:

Not applicable

Evidence for comparator:

Standard of care (standard surgical technique for GI anastomosis) used as comparator

Actual start date of recruitment	29 June 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	Belgium: 37
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	United States: 45
Country: Number of subjects enrolled	Australia: 25
Country: Number of subjects enrolled	New Zealand: 21
Country: Number of subjects enrolled	Korea, Republic of: 47
Worldwide total number of subjects	214
EEA total number of subjects	68

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)	124
From 65 to 84 years	89
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The first subject was recruited on the 29 June 2012 and last subject was 20 September 2013.

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. Inclusion criteria are detailed in Section 4 of the protocol.

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:

Actual treatment not discussed with the patient

Arms

Are arms mutually exclusive?	Yes
Arm title	Evicel Non randomized

Arm description:

Evicel Non randomized

Arm type	Non randomized run in
Investigational medicinal product name	Evicel
Investigational medicinal product code	Evicel
Other name	
Pharmaceutical forms	Sealant
Routes of administration	Topical use

Dosage and administration details:

At least 10mL of EVICEL (5mL BAC2 plus 5mL Human Thrombin) was to be dripped or sprayed around the circumference of the anastomotic staple line ensuring its full coverage with a layer of EVICEL of approximately 3mm in thickness and 1cm in width on either side of the staple line.

Arm title	Evicel Randomized

Arm description:

Evicel Randomized

Arm type	Active comparator
Investigational medicinal product name	Evicel
Investigational medicinal product code	Evicel
Other name	
Pharmaceutical forms	Sealant
Routes of administration	Topical use

Dosage and administration details:

At least 10mL of EVICEL (5mL BAC2 plus 5mL Human Thrombin) was to be dripped or sprayed around the circumference of the anastomotic staple line ensuring its full coverage with a layer of EVICEL of approximately 3mm in thickness and 1cm in width on either side of the staple line.

Arm title	Standard of care

Arm description:

Standard of care

Arm type	Standard of care

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Evicel Non randomized	Evicel Randomized	Standard of care
Started	41	84	89
Completed	40	80	86
Not completed	1	4	3
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	-	-	2
Lost to follow-up	-	1	-
Patient did not complete follow-up	-	2	-
Pt did not complete 90-day visit	1	-	-
Pt overseas and unable to be contacted	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Evicel Non randomized
Reporting group description: Evicel Non randomized	
Reporting group title	Evicel Randomized
Reporting group description: Evicel Randomized	
Reporting group title	Standard of care
Reporting group description: Standard of care	

Reporting group values	Evicel Non randomized	Evicel Randomized	Standard of care
Number of subjects	41	84	89
Age categorical Units: Subjects			
Adults (18-<50 years)	6	14	10
Adults (50-<65 years)	18	37	39
Adults (65-<75 years)	11	23	28
Adults (>=75 years)	6	10	12
Gender categorical Units: Subjects			
Female	21	41	33
Male	20	43	56

Reporting group values	Total		
Number of subjects	214		
Age categorical Units: Subjects			
Adults (18-<50 years)	30		
Adults (50-<65 years)	94		
Adults (65-<75 years)	62		
Adults (>=75 years)	28		
Gender categorical Units: Subjects			
Female	95		
Male	119		

End points

End points reporting groups

Reporting group title	Evicel Non randomized
Reporting group description: Evicel Non randomized	
Reporting group title	Evicel Randomized
Reporting group description: Evicel Randomized	
Reporting group title	Standard of care
Reporting group description: Standard of care	
Subject analysis set title	Intent to Treat (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT set was defined as all randomized subjects (with treatment defined by planned/randomized treatment).	
Subject analysis set title	Per Protocol (PP)
Subject analysis set type	Per protocol
Subject analysis set description: The PP set was defined as all subjects in the ITT set who had no major protocol deviations.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description: The safety set is defined as all subjects who received treatment.	

Primary: Absence of clinical anastomotic leak within 40 days post operatively

End point title	Absence of clinical anastomotic leak within 40 days post operatively[1]
End point description: Absence of clinical anastomotic leak within 40 days post operatively	
End point type	Primary
End point timeframe: Within 40 days post-operatively	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical data was provided for all the arms. The endpoint efficacy analysis was conducted using the intent-to-treat (ITT) set according to the protocol. The ITT included only all randomized subjects. Safety analysis set included all patients in the trial, which included non-randomized run-in patients.

End point values	Evicel Randomized	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	89		
Units: Absence of Leaks				
Absence of clinical anastomotic leak within 40 day	72	81		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

The primary efficacy endpoint was the absence of clinical anastomotic leak (success) within 40 days post operatively.

Comparison groups	Evicel Randomized v Standard of care
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.276
Method	Test of natural logarithm of odds ratio

Secondary: Incidence of clinical anastomotic leak up to post operative day 90

End point title	Incidence of clinical anastomotic leak up to post operative day 90[2]

End point description:

End point type	Secondary

End point timeframe:

Up to 90 days

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical data was provided for all the arms. The endpoint efficacy analysis was conducted using the intent-to-treat (ITT) set according to the protocol. The ITT included only all randomized subjects. Safety analysis set included all patients in the trial, which included non-randomized run-in patients.

End point values	Evicel Randomized	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	89		
Units: Leaks	9	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of stricture up to post operative day 90

End point title	Incidence of stricture up to post operative day 90[3]

End point description:

End point type	Secondary

End point timeframe:

Up to 90 days

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical data was provided for all the arms. The endpoint efficacy analysis was conducted using the intent-to-treat (ITT) set according to the protocol. The ITT included only all randomized subjects. Safety analysis set included all patients in the trial, which included non-randomized run-in patients.

End point values	Evicel Randomized	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	89		
Units: Number of strictures	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of post operative intervention related to clinical anastomotic leak or stricture up to post operative day 90

End point title	Incidence of post operative intervention related to clinical anastomotic leak or stricture up to post operative day 90[4]

End point description:

End point type	Secondary

End point timeframe:

Up to 90 days

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical data was provided for all the arms. The endpoint efficacy analysis was conducted using the intent-to-treat (ITT) set according to the protocol. The ITT included only all randomized subjects. Safety analysis set included all patients in the trial, which included non-randomized run-in patients.

End point values	Evicel Randomized	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	89		
Units: No. of subjects requiring intervention	9	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from the start of randomisation during the procedure, throughout the hospital admission, and until completion of the 90 day follow up visit (with the exception of incidence of stricture which was assessed up to Day 360)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	EVICEL Fibrin Sealant :Randomized
Reporting group description: -	
Reporting group title	Standard of Care
Reporting group description: -	
Reporting group title	EVICEL Fibrin Sealant Non Randomized
Reporting group description: -	

Serious adverse events	EVICEL Fibrin Sealant :Randomized	Standard of Care	EVICEL Fibrin Sealant Non Randomized
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 84 (29.76%)	22 / 89 (24.72%)	10 / 41 (24.39%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral cancer			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abscess drainage			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 84 (0.00%)	0 / 89 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 84 (2.38%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pelvic haematoma			
subjects affected / exposed	0 / 84 (0.00%)	0 / 89 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial secretion retention			
subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiccups			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			

subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 84 (1.19%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 84 (0.00%)	0 / 89 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood magnesium decreased			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anastomotic haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anastomotic leak			
subjects affected / exposed	9 / 84 (10.71%)	6 / 89 (6.74%)	3 / 41 (7.32%)
occurrences causally related to treatment / all	9 / 9	0 / 6	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anastomotic stenosis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intestinal anastomosis complication			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative ileus			
subjects affected / exposed	0 / 84 (0.00%)	3 / 89 (3.37%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound complication			
subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound evisceration			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 84 (0.00%)	0 / 89 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Critical illness polyneuropathy			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocutaneous fistula			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	3 / 84 (3.57%)	2 / 89 (2.25%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			

subjects affected / exposed	1 / 84 (1.19%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	0 / 89 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 84 (0.00%)	2 / 89 (2.25%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Portal vein thrombosis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

renal failure acute			
subjects affected / exposed	1 / 84 (1.19%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureteric stenosis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral stenosis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 84 (0.00%)	0 / 89 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal sepsis			
subjects affected / exposed	2 / 84 (2.38%)	2 / 89 (2.25%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	2 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess			
subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 89 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma infection			
subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
infectious peritonitis			
subjects affected / exposed	2 / 84 (2.38%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	1 / 84 (1.19%)	0 / 89 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic abscess			
subjects affected / exposed	2 / 84 (2.38%)	2 / 89 (2.25%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	2 / 84 (2.38%)	3 / 89 (3.37%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			

subjects affected / exposed	0 / 84 (0.00%)	0 / 89 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 84 (0.00%)	3 / 89 (3.37%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 84 (0.00%)	1 / 89 (1.12%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	EVICEL Fibrin Sealant :Randomized	Standard of Care	EVICEL Fibrin Sealant Non Randomized
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 84 (96.43%)	83 / 89 (93.26%)	41 / 41 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 84 (4.76%)	9 / 89 (10.11%)	3 / 41 (7.32%)
occurrences (all)	4	11	3
Hypotension			
subjects affected / exposed	13 / 84 (15.48%)	16 / 89 (17.98%)	5 / 41 (12.20%)
occurrences (all)	16	21	5
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 84 (8.33%)	3 / 89 (3.37%)	4 / 41 (9.76%)
occurrences (all)	7	4	7
Pain			
subjects affected / exposed	5 / 84 (5.95%)	10 / 89 (11.24%)	5 / 41 (12.20%)
occurrences (all)	7	10	6
Pyrexia			

subjects affected / exposed	15 / 84 (17.86%)	17 / 89 (19.10%)	9 / 41 (21.95%)
occurrences (all)	18	23	12
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 84 (5.95%)	3 / 89 (3.37%)	1 / 41 (2.44%)
occurrences (all)	5	3	1
Pleural effusion			
subjects affected / exposed	1 / 84 (1.19%)	5 / 89 (5.62%)	2 / 41 (4.88%)
occurrences (all)	1	5	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 84 (5.95%)	3 / 89 (3.37%)	2 / 41 (4.88%)
occurrences (all)	5	3	2
Insomnia			
subjects affected / exposed	7 / 84 (8.33%)	7 / 89 (7.87%)	6 / 41 (14.63%)
occurrences (all)	7	8	8
Investigations			
C-reactive protein increased			
subjects affected / exposed	4 / 84 (4.76%)	6 / 89 (6.74%)	0 / 41 (0.00%)
occurrences (all)	4	6	0
Oxygen saturation decreased			
subjects affected / exposed	6 / 84 (7.14%)	1 / 89 (1.12%)	1 / 41 (2.44%)
occurrences (all)	6	1	2
Urine output decreased			
subjects affected / exposed	7 / 84 (8.33%)	10 / 89 (11.24%)	2 / 41 (4.88%)
occurrences (all)	9	11	2
White blood cell count increased			
subjects affected / exposed	5 / 84 (5.95%)	2 / 89 (2.25%)	1 / 41 (2.44%)
occurrences (all)	6	3	1
Injury, poisoning and procedural complications			
Anastomotic leak			
subjects affected / exposed	9 / 84 (10.71%)	6 / 89 (6.74%)	3 / 41 (7.32%)
occurrences (all)	9	6	3
Incision site pain			
subjects affected / exposed	3 / 84 (3.57%)	3 / 89 (3.37%)	6 / 41 (14.63%)
occurrences (all)	4	3	7

Procedural pain			
subjects affected / exposed	19 / 84 (22.62%)	17 / 89 (19.10%)	6 / 41 (14.63%)
occurrences (all)	20	19	6
Wound complication			
subjects affected / exposed	5 / 84 (5.95%)	2 / 89 (2.25%)	0 / 41 (0.00%)
occurrences (all)	5	2	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	6 / 84 (7.14%)	12 / 89 (13.48%)	4 / 41 (9.76%)
occurrences (all)	7	14	6
Ileus			
subjects affected / exposed	6 / 84 (7.14%)	5 / 89 (5.62%)	1 / 41 (2.44%)
occurrences (all)	6	5	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 84 (5.95%)	9 / 89 (10.11%)	4 / 41 (9.76%)
occurrences (all)	5	12	5
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 84 (3.57%)	5 / 89 (5.62%)	2 / 41 (4.88%)
occurrences (all)	3	6	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 84 (3.57%)	5 / 89 (5.62%)	4 / 41 (9.76%)
occurrences (all)	4	5	4
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	12 / 84 (14.29%)	17 / 89 (19.10%)	5 / 41 (12.20%)
occurrences (all)	14	19	6
Abdominal pain			
subjects affected / exposed	17 / 84 (20.24%)	17 / 89 (19.10%)	8 / 41 (19.51%)
occurrences (all)	20	23	8
Constipation			
subjects affected / exposed	14 / 84 (16.67%)	17 / 89 (19.10%)	11 / 41 (26.83%)
occurrences (all)	15	19	12
Diarrhoea			
subjects affected / exposed	11 / 84 (13.10%)	15 / 89 (16.85%)	8 / 41 (19.51%)
occurrences (all)	11	18	12

Nausea			
subjects affected / exposed	42 / 84 (50.00%)	47 / 89 (52.81%)	22 / 41 (53.66%)
occurrences (all)	63	65	43
Proctalgia			
subjects affected / exposed	3 / 84 (3.57%)	5 / 89 (5.62%)	1 / 41 (2.44%)
occurrences (all)	5	5	1
Rectal haemorrhage			
subjects affected / exposed	3 / 84 (3.57%)	5 / 89 (5.62%)	4 / 41 (9.76%)
occurrences (all)	3	6	4
Vomiting			
subjects affected / exposed	20 / 84 (23.81%)	22 / 89 (24.72%)	11 / 41 (26.83%)
occurrences (all)	29	26	14
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	9 / 84 (10.71%)	8 / 89 (8.99%)	6 / 41 (14.63%)
occurrences (all)	10	8	7
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	3 / 84 (3.57%)	5 / 89 (5.62%)	2 / 41 (4.88%)
occurrences (all)	3	5	2
Urinary retention			
subjects affected / exposed	3 / 84 (3.57%)	5 / 89 (5.62%)	0 / 41 (0.00%)
occurrences (all)	3	5	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	5 / 84 (5.95%)	11 / 89 (12.36%)	1 / 41 (2.44%)
occurrences (all)	5	15	1
Wound infection			
subjects affected / exposed	2 / 84 (2.38%)	5 / 89 (5.62%)	4 / 41 (9.76%)
occurrences (all)	3	5	4
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 84 (9.52%)	6 / 89 (6.74%)	2 / 41 (4.88%)
occurrences (all)	10	6	2
Hypokalaemia			
subjects affected / exposed	5 / 84 (5.95%)	9 / 89 (10.11%)	5 / 41 (12.20%)
occurrences (all)	5	11	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2012	1) Clarity on measurement of level of anastomosis 2) Exclusion criteria updated 3) Stopping rules included
09 May 2013	Several protocol clarifications and expansion of visit windows to allow for standard follow up visits to align with study visits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported