Clinical trial results:
A Prospective, Randomized Controlled Study to Compare the Effects of a Fibrin Sealant(FS2) Versus Manual Compression on Haemostatic Efficacy During Vascular Surgical Procedures Utilising Polytetrafluorethylene Graft Material on an End-to-Side Femoral or Upper Extremity Vascular Access Arterial Anastomosis.

Summary

EudraCT number	2005-000889-39
Trial protocol	GB
Global end of trial date	29 March 2006

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	400-05-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00154141
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., 1 9082182492, jbatill2@its.jnj.com
Scientific contact	Jonathan Batiller, 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	11 April 2006
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 March 2006
Global end of trial reached?	Yes
Global end of trial date	29 March 2006
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate whether the fibrin sealant (FS2) reduces time to haemostasis during vascular surgical procedure on an end-to-side femoral or upper extremity arterial anastomosis utilising uncoated or heparin-coated polytetrafluoroethylene (PTFE) compared to manual compression (MC). Success rate of the FS2 group will be compared to success rate of the Manual Compression group. Success will be defined as the absence of bleeding at 4 minutes following randomisation.

Protection of trial subjects:

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

Background therapy:

Not applicable

Evidence for comparator:

Manual compression was used as a comparator. Traditionally suture hole bleeding was managed by compression with surgical swabs and reversal of heparin.

Actual start date of recruitment	09 June 2005
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 States: 102
Country: Number of subjects enrolled	United Kingdom: 45
Worldwide total number of subjects	147
EEA total number of subjects	45

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)	58
From 65 to 84 years	86
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The first subject was randomized 09-Jun-2005 and the last subject completed 29-Mar-2006. Patients were recruited from UK and US sites.

Pre-assignment

Screening details:

Prospective subjects were screened within 21 days prior to surgery. Prior to any study-related procedures being undertaken subjects were fully informed of all aspects of the study including the benefits, risks and constraints 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:

No blinding

Arms

Are arms mutually exclusive?	Yes
Arm title	FS2 product

Arm description:

FS2

Arm type	Experimental
Investigational medicinal product name	FS2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sealant
Routes of administration	Topical use

Dosage and administration details:

One FS2 kit contained the two components in separate vials (2 x 2 ml). The two components were:
- Biological Active Component 2 (BAC2), comprising human fibrinogen 55-85 mg/ml
- Thrombin comprising human thrombin 800-1200 IU/ml and calcium chloride 5.6-6.2 mg/ml.

For each patient, one kit of FS2 (2 ml each of BAC2 and Thrombin [total 4 ml]) was pre-prepared for administration prior to randomisation and was administered by dripping onto the study anastomotic site (SAS).

Arm title	Manual compression

Arm description:

Manual compression

Arm type	Manual compression

No investigational medicinal product assigned in this arm

Number of subjects in period 1	FS2 product	Manual compression
Started	75	72
Completed	73	69
Not completed	2	3
Adverse event, serious fatal	1	1
Lost to follow-up	1	2

Baseline characteristics

Reporting groups	
Reporting group title	FS2 product
Reporting group description: FS2	
Reporting group title	Manual compression
Reporting group description: Manual compression	

Reporting group values	FS2 product	Manual compression	Total
Number of subjects	75	72	147
Age categorical Units: Subjects			
< 50 years	5	13	18
50-64 years	27	13	40
65-74 years	26	27	53
>=75 years	17	19	36
Gender categorical Units: Subjects			
Female	34	36	70
Male	41	36	77

End points

End points reporting groups	
Reporting group title	FS2 product
Reporting group description: FS2	
Reporting group title	Manual compression
Reporting group description: Manual compression	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: The Full Analysis Set (FAS) comprised all randomised subjects (equivalent to the intent-to-treat (ITT) set).	

Primary: Absence of bleeding at SAS 4 minutes following randomisation	
End point title	Absence of bleeding at SAS 4 minutes following randomisation
End point description: Absence of bleeding at SAS 4 minutes following randomisation	
End point type	Primary
End point timeframe: 4 minutes following randomisation	

End point values	FS2 product	Manual compression	Full Analysis Set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	75	72	147	
Units: Absence of bleeding	64	28	147	

Statistical analyses

Statistical analysis title	Primary efficacy endpoint
Comparison groups	Manual compression v FS2 product
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.7
upper limit	27.5

Secondary: Absence of bleeding at SAS 7 minutes following randomisation	
End point title	Absence of bleeding at SAS 7 minutes following randomisation
End point description: Absence of bleeding at SAS 7 minutes following randomisation	
End point type	Secondary
End point timeframe: 7 minutes following randomisation	

End point values	FS2 product	Manual compression		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	72		
Units: Absence of bleeding	68	43		

Statistical analyses

Statistical analysis title	secondary endpoint analysis
Comparison groups	FS2 product v Manual compression
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	logistics model
Parameter estimate	Log odds ratio
Point estimate	7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	21.9

Secondary: Absence of bleeding at SAS 10 minutes following randomisation	
End point title	Absence of bleeding at SAS 10 minutes following randomisation
End point description: Absence of bleeding at SAS 10 minutes following randomisation	
End point type	Secondary
End point timeframe: 10 minutes following randomisation	

End point values	FS2 product	Manual compression		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	72		
Units: Absence of bleeding	72	50		

Statistical analyses

Statistical analysis title	Secondary Endpoint Analysis
Comparison groups	FS2 product v Manual compression
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	logistic model
Parameter estimate	Log odds ratio
Point estimate	18.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.7
upper limit	91.8

Secondary: Incidence of potential bleeding related complications	
End point title	Incidence of potential bleeding related complications
End point description: Incidence of potential bleeding related complications	
End point type	Secondary
End point timeframe: 5 weeks post surgery (+/- 7 days	

End point values	FS2 product	Manual compression		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	72		
Units: bleeding related complications	12	15		

Statistical analyses

Statistical analysis title	Secondary endpoint
Statistical analysis description: Potential bleeding related complications	
Comparison groups	FS2 product v Manual compression
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.426
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	3.7

Secondary: Incidence of treatment failure.	
End point title	Incidence of treatment failure.
End point description: Incidence of treatment failure.	
End point type	Secondary
End point timeframe: 5 weeks post surgery (+/- 7 days)	

End point values	FS2 product	Manual compression		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	72		
Units: treatment failure	6	23		

Statistical analyses

Statistical analysis title	Secondary endpoint
Statistical analysis description: Incidence of treatment failure	
Comparison groups	FS2 product v Manual compression
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.001
Method	Logistic model
Parameter estimate	Odds ratio (OR)
Point estimate	0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.5

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE's were collected from the start of the Baseline Visit throughout the hospital admission for the procedure and until completion of the 5-week Follow-up Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	8.1

Reporting groups

Reporting group title	FS2 product

Reporting group description:

FS2

Reporting group title	Manual compression

Reporting group description:

Manual compression

Serious adverse events	FS2 product	Manual compression	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 75 (30.67%)	21 / 72 (29.17%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	1 / 75 (1.33%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic occlusion			

subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (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			
Respiratory failure			
subjects affected / exposed	1 / 75 (1.33%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium tremens			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood glucose increased			

subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Vascular graft occlusion			
subjects affected / exposed	1 / 75 (1.33%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft thrombosis			
subjects affected / exposed	3 / 75 (4.00%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site haemorrhage			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ventricular tachycardia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 75 (0.00%)	4 / 72 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myocardial infarction			
subjects affected / exposed	0 / 75 (0.00%)	2 / 72 (2.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intestinal fistula			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure chronic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (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			
Muscular weakness			

subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (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			
Localised infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 75 (1.33%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Graft infection			
subjects affected / exposed	3 / 75 (4.00%)	4 / 72 (5.56%)	
occurrences causally related to treatment / all	2 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Wound infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural cellulitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			

subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (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			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	FS2 product	Manual compression	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 75 (64.00%)	51 / 72 (70.83%)	
Injury, poisoning and procedural complications			
Vascular graft occlusion			
subjects affected / exposed	2 / 75 (2.67%)	5 / 72 (6.94%)	
occurrences (all)	2	5	
Graft thrombosis			
subjects affected / exposed	5 / 75 (6.67%)	0 / 72 (0.00%)	
occurrences (all)	6	0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 75 (1.33%)	5 / 72 (6.94%)	
occurrences (all)	1	5	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 75 (0.00%)	5 / 72 (6.94%)	
occurrences (all)	0	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 75 (0.00%)	5 / 72 (6.94%)	
occurrences (all)	0	5	
General disorders and administration site conditions			

Oedema peripheral subjects affected / exposed occurrences (all)	5 / 75 (6.67%) 5	2 / 72 (2.78%) 2	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	2 / 75 (2.67%) 2 2 / 75 (2.67%) 2	6 / 72 (8.33%) 6 5 / 72 (6.94%) 6	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) Graft infection subjects affected / exposed occurrences (all)	1 / 75 (1.33%) 1 4 / 75 (5.33%) 4	4 / 72 (5.56%) 4 5 / 72 (6.94%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2005	Amendment 2- Following an investigator meeting clarification was provided on exclusion criterion one, measuring of intra-operative blood loss at the SAS was removed, a smaller dose of heparin was required for subjects undergoing an upper extremity procedure and clarification was added regarding prohibiting the use of any other fibrin sealant.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 September 2005	Recruitment into the study was temporarily suspended between Monday 26th September 2005 and Monday 10th October 2005 for reasons related to the CE-marked application device that is used to apply the Investigational Product. The company realized that there were two different productions of the vial connector of the application device . One production had two moulding holes and the other production did not. After a comprehensive analysis of the two vial connectors, the company concluded that there was no clinical or safety impact from the variation.	10 October 2005

Notes:

Limitations and caveats

None reported