Clinical trial results:
A Prospective, Single-blind, Randomized, Phase II/III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Hemostasis During Peripheral Vascular Surgery

Summary

EudraCT number	2008-000072-25
Trial protocol	ES GB
Global end of trial date	05 May 2014

Results information

Result version number	v1 (current)
This version publication date	01 July 2016
First version publication date	01 July 2016

Trial information

Trial identification

Sponsor protocol code	IG402

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00684047
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Instituto Grifols, S.A.
Sponsor organisation address	Can Guasch, Parets del Vallés, Spain, 08150
Public contact	Paul Pinciaro, Instituto Grifols, S.A., 1 443-375-8825, Paul.Pinciaro@grifols.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001598-PIP01-13
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	05 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 May 2014
Global end of trial reached?	Yes
Global end of trial date	05 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and hemostasis effectiveness of human plasma-derived fibrin sealant Grifols (FS Grifols) in peripheral vascular surgery

Protection of trial subjects:

For each investigative site, the Primary Part (II) started only after the enrollment of at least 2 subjects in the Preliminary Part (I). In addition, for any trial site, the Primary Part (II) could start only after the enrollment of a set of at least 20 subjects at any site(s) into the Preliminary Part (I), with no safety issues raised by the independent Medical Monitor. As requested by the Main Research Ethics Committee for the study in the UK, trial sites in the UK had the additional requirement that the Data Safety Monitoring Board (DSMB) raised no safety issues that recommended against starting the Primary Part (II) in the UK. Further, at any trial site, the Primary Part (II) could not begin until formally approved for each country by the Sponsor.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 78
Country: Number of subjects enrolled	United Kingdom: 117
Country: Number of subjects enrolled	Canada: 44
Worldwide total number of subjects	239
EEA total number of subjects	195

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)	79
From 65 to 84 years	153
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Study Initiation Date: 20 October 2008; Study Completion Date: 05 May 2014
Nineteen sites were initiated in Canada, Spain, and the United Kingdom (UK). From these, 18 sites enrolled patients.

Pre-assignment

Screening details:

A total of 371 subjects were enrolled in the study (signed informed consent). Of these, 240 (64.7%) subjects complied with eligibility criteria and underwent vascular surgery.

Pre-assignment period milestones

Number of subjects started	371[1]
Number of subjects completed	239

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 2
Reason: Number of subjects	Adverse event, serious fatal: 9
Reason: Number of subjects	Lost to follow-up: 7
Reason: Number of subjects	Consent withdrawn by subject: 15
Reason: Number of subjects	Screening failures: 98
Reason: Number of subjects	Dropout after randomize & prior to treatment: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The worldwide number of subjects enrolled in the trial is the same as the total number of subjects at the end of the pre-assignment period. The patients that did not complete the pre-assignment period are those that were screening failures and were not enrolled in the trial, due to different reasons.

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:

In the Preliminary Part (I) of the study, all subjects were treated with FS Grifols. In the Primary Part (II) of the study, subjects were blinded to their study treatment, but the Investigator was not blinded as this was not feasible due to the very different nature of the 2 hemostatic treatments to be applied.
Treatment group assignments were made using sealed blinded randomization envelopes that were only opened upon identification of an eligible TBS during the procedure.

Arms

Are arms mutually exclusive?	Yes
Arm title	Preliminary Part (I) - FS Grifols

Arm description:

All subjects enrolled in the Preliminary Part (I) were treated with FS Grifols. This part of the trial had 2 main objectives:
1) To ensure that local study teams familiarized themselves with the technique of FS Grifols application and with the intra-operative procedures required by the protocol. To meet this objective, the first 2 subjects at each site were enrolled and treated with FS Grifols.
2) To assess the clinical safety of FS Grifols. Treatment of 20 subjects with FS Grifols was considered sufficient for an initial assessment of clinical safety.

Arm type	Experimental
Investigational medicinal product name	Fibrin Sealant Grifols
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for sealant
Routes of administration	Topical use

Dosage and administration details:

Up to two 3-mL kits applied topically via drip applicator tip at the target bleeding site (TBS)

Arm title	Primary Part (II) - FS Grifols

Arm description:

In the Primary Part (II), subjects were randomly assigned 2:1 to treatment with Fibrin Sealant Grifols or Manual Compression, respectively.

Arm type	Experimental
Investigational medicinal product name	Fibrin Sealant Grifols
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for sealant
Routes of administration	Topical use

Dosage and administration details:

Up to two 3-ml kits applied topically via drip applicator tip at the target bleeding site (TBS).

Arm title	Primary Part (II) - Manual compression

Arm description:

In the Primary Part (II), subjects were randomly assigned 2:1 to treatment with Fibrin Sealant Grifols or Manual Compression, respectively.
Subjects randomized to Manual Compression received application of manual compression with surgical gauzes at the target bleeding site (TBS).

Arm type	hemostatic action considered standard &effective

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Preliminary Part (I) - FS Grifols	Primary Part (II) - FS Grifols	Primary Part (II) - Manual compression
Started	72	110	57
Completed	59	94	52
Not completed	13	16	5
Adverse event, serious fatal	6	2	1
Consent withdrawn by subject	4	9	2
loss of contact	1	-	-
Lost to follow-up	1	5	1
Protocol deviation	1	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Preliminary Part (I) - FS Grifols
Reporting group description:	
All subjects enrolled in the Preliminary Part (I) were treated with FS Grifols. This part of the trial had 2 main objectives: 1) To ensure that local study teams familiarized themselves with the technique of FS Grifols application and with the intra-operative procedures required by the protocol. To meet this objective, the first 2 subjects at each site were enrolled and treated with FS Grifols. 2) To assess the clinical safety of FS Grifols. Treatment of 20 subjects with FS Grifols was considered sufficient for an initial assessment of clinical safety.	
Reporting group title	Primary Part (II) - FS Grifols
Reporting group description:	
In the Primary Part (II), subjects were randomly assigned 2:1 to treatment with Fibrin Sealant Grifols or Manual Compression, respectively.	
Reporting group title	Primary Part (II) - Manual compression
Reporting group description:	
In the Primary Part (II), subjects were randomly assigned 2:1 to treatment with Fibrin Sealant Grifols or Manual Compression, respectively. Subjects randomized to Manual Compression received application of manual compression with surgical gauzes at the target bleeding site (TBS).	

Reporting group values	Preliminary Part (I) - FS Grifols	Primary Part (II) - FS Grifols	Primary Part (II) - Manual compression
Number of subjects	72	110	57
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	20	34	25
From 65-84 years	52	72	29
85 years and over	0	4	3
Age continuous			
Units: years			
median	70	69	67
inter-quartile range (Q1-Q3)	63 to 75	63 to 74	59 to 75
Gender categorical			
Units: Subjects			
Female	17	15	18
Male	55	95	39

Reporting group values	Total		
Number of subjects	239		
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)	79		
From 65-84 years	153		
85 years and over	7		
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical			
Units: Subjects			
Female	50		
Male	189		

End points

End points reporting groups

Reporting group title	Preliminary Part (I) - FS Grifols

Reporting group description:

All subjects enrolled in the Preliminary Part (I) were treated with FS Grifols. This part of the trial had 2 main objectives:
1) To ensure that local study teams familiarized themselves with the technique of FS Grifols application and with the intra-operative procedures required by the protocol. To meet this objective, the first 2 subjects at each site were enrolled and treated with FS Grifols.
2) To assess the clinical safety of FS Grifols. Treatment of 20 subjects with FS Grifols was considered sufficient for an initial assessment of clinical safety.

Reporting group title	Primary Part (II) - FS Grifols

Reporting group description:

In the Primary Part (II), subjects were randomly assigned 2:1 to treatment with Fibrin Sealant Grifols or Manual Compression, respectively.

Reporting group title	Primary Part (II) - Manual compression

Reporting group description:

In the Primary Part (II), subjects were randomly assigned 2:1 to treatment with Fibrin Sealant Grifols or Manual Compression, respectively.
Subjects randomized to Manual Compression received application of manual compression with surgical gauzes at the target bleeding site (TBS).

Subject analysis set title	Preliminary Part (I) - FS Grifols (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

In the Preliminary Part (I), the intent-to-treat (ITT) analysis set was defined asall subjects who underwent surgery and met the intra-operative inclusion criterion.

Subject analysis set title	Primary Part (II) - FS Grifols (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

In the Primary Part (II), intent-to-treat (ITT) analysis set was defined as all subjects who underwent surgery, met the intra-operative inclusion criterion, had a randomization envelope opened, and still met the intra-operative inclusion criterion after randomization.

Subject analysis set title	Primary Part (II) - Manual Compression (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

In the Primary Part (II), intent-to-treat (ITT) analysis set was defined as all subjects who underwent surgery, met the intra-operative inclusion criterion, had a randomization envelope opened, and still met the intra-operative inclusion criterion after randomization.

Subject analysis set title	Preliminary Part (I) - FS Grifols (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population was defined as the ITT population excluding any subjects who did not actually receive either study treatment or who had a major protocol violation.
Major protocol violations and the final PP population were determined before database lock.

Subject analysis set title	Primary Part (II) - FS Grifols (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population was defined as the ITT population excluding any subjects who did not actually receive either study treatment or who had a major protocol violation.
Major protocol violations and the final PP population were determined before database lock.

Subject analysis set title	Primary Part (II) - Manual Compression (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population was defined as the ITT population excluding any subjects who did not actually receive either study treatment or who had a major protocol violation.
Major protocol violations and the final PP population were determined before database lock.

Primary: Time to Hemostasis (TTH)

End point title	Time to Hemostasis (TTH)

End point description:

The precise TTH was not observable in this study. However, if hemostasis had not been achieved at a given assessment time point, but had been achieved at the next assessment time point, then it was inferred that the true TTH was between the 2 assessment time points. Therefore, TTH, although not observed directly, was ascertained as falling into 1 of 5 hemostatic time categories (HTCs) or the non-HTC as follows:
1. HTC≤3: ≤3 minutes from TStart to hemostasis.
2. HTC>3 to ≤4: >3 minutes to ≤4 minutes from TStart to hemostasis.
3. HTC>4 to ≤5: >4 minutes to ≤5 minutes from TStart to hemostasis.
4. HTC>5 to ≤7: >5 minutes to ≤7 minutes from TStart to hemostasis.
5. HTC>7 to ≤10: >7 minutes to ≤10 minutes from TStart to hemostasis.
Treatment failure includes: brisk bleeding from the TBS during the 10 minutes observational period, TTH > 10 minutes and re-bleeding from the TBS before surgical closure of the field containing the TBS

End point type	Primary

End point timeframe:

TTH is measured in minutes from the start of treatment application (TStart) at the Target Bleeding Site (TBS) to the achievement of hemostasis at that site or to the end of the 10-minute observational period if hemostasis has not yet been achieved.

End point values	Preliminary Part (I) - FS Grifols (ITT)	Primary Part (II) - FS Grifols (ITT)	Primary Part (II) - Manual Compression (ITT)	Preliminary Part (I) - FS Grifols (PP)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	72	110	57	57
Units: subjects				
TTH ≤ 3 minutes	41	51	15	32
TTH > 3 but ≤ 4 minutes	11	18	3	8
TTH > 4 but ≤ 5 minutes	5	13	10	4
TTH > 5 but ≤ 7 minutes	3	5	4	3
TTH > 7 but ≤ 10 minutes	5	10	9	4
Treatment failures	7	13	16	6

End point values	Primary Part (II) - FS Grifols (PP)	Primary Part (II) - Manual Compression (PP)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	48		
Units: subjects				
TTH ≤ 3 minutes	40	13		
TTH > 3 but ≤ 4 minutes	13	3		
TTH > 4 but ≤ 5 minutes	12	6		
TTH > 5 but ≤ 7 minutes	3	3		
TTH > 7 but ≤ 10 minutes	7	7		
Treatment failures	11	16		

Statistical analyses

Statistical analysis title	Primary efficacy endpoint analysis (ITT)
Comparison groups	Primary Part (II) - FS Grifols (ITT) v Primary Part (II) - Manual Compression (ITT)
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Primary efficacy endpoint analysis (PP)
Comparison groups	Primary Part (II) - FS Grifols (PP) v Primary Part (II) - Manual Compression (PP)
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Secondary: Cumulative proportion of subjects achieving hemostasis at TBS at each of the 5 HTCs

End point title	Cumulative proportion of subjects achieving hemostasis at TBS at each of the 5 HTCs

End point description:

End point type	Secondary

End point timeframe:

From the start of treatment application (TStart) at the Target Bleeding Site to the achievement of hemostasis at that site or to the end of the 10-minute observational period if hemostasis has not yet been achieved.

End point values	Preliminary Part (I) - FS Grifols (ITT)	Primary Part (II) - FS Grifols (ITT)	Primary Part (II) - Manual Compression (ITT)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	72	110	57	
Units: percent				
number (not applicable)				
TTH ≤ 3 minutes	56.9	46.4	26.3	
TTH ≤ 4 minutes	72.2	62.7	31.6	
TTH ≤ 5 minutes	79.2	74.5	49.1	
TTH ≤ 7 minutes	83.3	79.1	56.1	
TTH ≤ 10 minutes	90.3	88.2	71.9	

Statistical analyses

Statistical analysis title	Proportions of subjects achieving hemostasis
Comparison groups	Primary Part (II) - FS Grifols (ITT) v Primary Part (II) - Manual Compression (ITT)
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013 [1]
Method	Fisher exact

Notes:

[1] - TTH ≤3 minutes: p = 0.013.
TTH ≤4 minutes (cumulative): p < 0.001.
TTH ≤5 minutes (cumulative): p = 0.002.
TTH ≤7 minutes (cumulative): p = 0.004.
TTH ≤10 minutes (cumulative): p = 0.016.

Secondary: Prevalence of treatment failures

End point title	Prevalence of treatment failures

End point description:

Reasons for treatment failure:

Brisk bleeding from the target bleeding site
Time to hemostasis > 10 minutes
Re-bleeding after 10 minutes observational period and before closure

End point type	Secondary

End point timeframe:

From the Tstart until the completion (when the last skin closure stitch is placed) of the surgical closure by layers of the exposed surgical field containing the TBS (TClosure).

End point values	Preliminary Part (I) - FS Grifols (ITT)	Primary Part (II) - FS Grifols (ITT)	Primary Part (II) - Manual Compression (ITT)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	72	110	57	
Units: percent				
number (not applicable)				
Brisk bleeding from the target bleeding site	4.2	5.5	8.8	
Time to hemostasis > 10 min	1.4	4.5	17.5	
Re-bleeding after 10 min and before closure	4.2	1.8	1.8	
Total	9.7	11.8	28.1	

Statistical analyses

Statistical analysis title	Prevalence of treatment failures
Comparison groups	Primary Part (II) - FS Grifols (ITT) v Primary Part (II) - Manual Compression (ITT)
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Subjects were monitored from the time of the signature of the informed consent to Post-Operative Week 6 ± 4 Days for assessment of Adverse Events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	FS Grifols [pooled Preliminary Part (I) + Primary Part (II)]

Reporting group description:

Subjects from the Preliminary Part (I) and from the Primary Part (II) of the study treated with Fibrin Sealant Grifols have been pooled for summarizing safety data of the study.
This reporting group includes subjects randomized to Manual Compression but received Fibrin Sealant Grifols by mistake.

Reporting group title	Manual Compression Primary Part (II)

Reporting group description:

Subjects randomized to Manual Compression treatment in the Primary Part (II) of the study.

Serious adverse events	FS Grifols [pooled Preliminary Part (I) + Primary Part (II)]	Manual Compression Primary Part (II)	
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 187 (25.13%)	9 / 52 (17.31%)	
number of deaths (all causes)	7	1	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Graft haemorrhage			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Operative haemorrhage			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 187 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Post procedural haemorrhage			
subjects affected / exposed	2 / 187 (1.07%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	0 / 187 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft occlusion			
subjects affected / exposed	2 / 187 (1.07%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	2 / 187 (1.07%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 187 (0.53%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 187 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	2 / 187 (1.07%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 187 (1.07%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 187 (1.07%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 187 (1.07%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 187 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	2 / 187 (1.07%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 187 (1.07%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Transient ischemic attack			
subjects affected / exposed	2 / 187 (1.07%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiorgan failure			
subjects affected / exposed	0 / 187 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	0 / 187 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastritis			
subjects affected / exposed	0 / 187 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernial eventration			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	0 / 187 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	2 / 187 (1.07%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (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			
Haematuria			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 187 (1.07%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure chronic			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (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			
Abdominal sepsis			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	0 / 187 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	2 / 187 (1.07%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post operative wound infection			
subjects affected / exposed	4 / 187 (2.14%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 187 (1.07%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	3 / 187 (1.60%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 187 (0.53%)	0 / 52 (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	FS Grifols [pooled Preliminary Part (I) + Primary Part (II)]	Manual Compression Primary Part (II)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	151 / 187 (80.75%)	45 / 52 (86.54%)	
Investigations			
Blood potassium decreased			

subjects affected / exposed	12 / 187 (6.42%)	5 / 52 (9.62%)	
occurrences (all)	13	5	
Blood magnesium decreased			
subjects affected / exposed	5 / 187 (2.67%)	3 / 52 (5.77%)	
occurrences (all)	5	3	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	112 / 187 (59.89%)	36 / 52 (69.23%)	
occurrences (all)	113	36	
Vascular disorders			
Hypotension			
subjects affected / exposed	32 / 187 (17.11%)	8 / 52 (15.38%)	
occurrences (all)	34	8	
Haematoma			
subjects affected / exposed	7 / 187 (3.74%)	3 / 52 (5.77%)	
occurrences (all)	8	4	
Hypertension			
subjects affected / exposed	7 / 187 (3.74%)	3 / 52 (5.77%)	
occurrences (all)	8	3	
Nervous system disorders			
Hypoaesthesia			
subjects affected / exposed	3 / 187 (1.60%)	3 / 52 (5.77%)	
occurrences (all)	3	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 187 (8.56%)	1 / 52 (1.92%)	
occurrences (all)	17	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	14 / 187 (7.49%)	3 / 52 (5.77%)	
occurrences (all)	15	3	
Oedema peripheral			
subjects affected / exposed	9 / 187 (4.81%)	5 / 52 (9.62%)	
occurrences (all)	9	5	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	44 / 187 (23.53%)	10 / 52 (19.23%)	
occurrences (all)	51	11	
Constipation			
subjects affected / exposed	39 / 187 (20.86%)	8 / 52 (15.38%)	
occurrences (all)	39	8	
Vomiting			
subjects affected / exposed	14 / 187 (7.49%)	6 / 52 (11.54%)	
occurrences (all)	25	6	
Abdominal pain			
subjects affected / exposed	8 / 187 (4.28%)	3 / 52 (5.77%)	
occurrences (all)	8	4	
Diarrhoea			
subjects affected / exposed	10 / 187 (5.35%)	2 / 52 (3.85%)	
occurrences (all)	12	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 187 (3.74%)	3 / 52 (5.77%)	
occurrences (all)	7	3	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	14 / 187 (7.49%)	3 / 52 (5.77%)	
occurrences (all)	14	3	
Postoperative wound infection			
subjects affected / exposed	11 / 187 (5.88%)	2 / 52 (3.85%)	
occurrences (all)	11	2	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	11 / 187 (5.88%)	3 / 52 (5.77%)	
occurrences (all)	12	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2010	Balanced the ratio of grafts enrolled in the Primary Part (II) of the study: in order to achieve a similar representation of both types of graft (PTFE or Dacron), after the enrollment of approximately 90 subjects with one of both types of graft (PTFE or Dacron), the Sponsor of the clinical trial permitted enrollment of only subjects with the other type of graft into the Primary Part (II) of the study. Added femoral endarterectomy with patch angioplasty and ilio-femoral bypass grafting as acceptable surgical procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported