



Clinical trial results:

A Prospective, Single-blind, Randomized, Phase 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	2013-005127-16
Trial protocol	HU
Global end of trial date	26 December 2015

Results information

Result version number	v1 (current)
This version publication date	06 August 2017
First version publication date	06 August 2017

Trial information

Trial identification

Sponsor protocol code	IG1101
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01662856
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Instituto Grifols, S.A.
Sponsor organisation address	Can Guasch, 2, Parets del Vallès, Spain, 08150
Public contact	Department of Clinical Trials, Instituto Grifols, S.A., +34 935712200, IGregulatory.affairs@grifols.com
Scientific contact	Department of Clinical Trials, Instituto Grifols, S.A., +34 935712200, IGregulatory.affairs@grifols.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-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	15 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 December 2015
Global end of trial reached?	Yes
Global end of trial date	26 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and the hemostasis efficacy 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 2 subjects in the Preliminary Part (I).

Further, all SAEs must have been expeditiously reported, whether or not considered attributable to the study treatment. When the investigator became aware of an SAE, a completed, signed, and dated SAE Report Form must have been submitted within 24 hours to the sponsor.

After the initial report, all relevant information for SAE follow-up and the outcome must have also been supplied to the sponsor in a timely manner (within 3 days from its identification or within 24 hours for relevant new information) by means of the SAE Report

Form or by other appropriate means such as data clarification forms issued by the sponsor or CRO.

SAEs were assessed by the sponsor for expectedness assuming that all subjects were treated with FS Grifols. If the event was considered serious, potentially related, and unexpected, treatment allocation would have been unblinded. Three possibilities resulting from the procedure of unblinding would have been considered:

1. If the study treatment administered to the subject was FS Grifols, the case would be reported in accordance to local regulations.
2. If the study treatment administered to the subject was MC, the event would be reassessed for expectedness according to the reference safety information and:
 - a. If the event was still considered unexpected, it would have been reported in accordance with applicable requirements and guidelines.
 - b. If the event was considered expected, it would not have been reported, unless specifically requested by local regulations.

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	02 August 2012
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	Hungary: 72
Country: Number of subjects enrolled	United States: 85
Country: Number of subjects enrolled	Serbia: 47

Country: Number of subjects enrolled	Russian Federation: 21
Worldwide total number of subjects	225
EEA total number of subjects	72

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)	122
From 65 to 84 years	103
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study initiation date: 02 Aug 2012; Study completion date: 26 Dec 2015

Subjects were recruited from USA, Hungary, Serbia and Russia.

Pre-assignment

Screening details:

A total of 283 subjects were screened in this study. Of these, 225 subjects were randomized and 58 were screen failures.

Pre-assignment period milestones

Number of subjects started	283 ^[1]
Number of subjects completed	225

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 3
Reason: Number of subjects	Physician decision: 2
Reason: Number of subjects	Protocol deviation: 2
Reason: Number of subjects	Inclusion/exclusion criteria not met: 39
Reason: Number of subjects	Other: 12

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: total 58 subjects were screen failures so can not continue with enrollment.

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, all subjects were treated with FS Grifols. In the Primary Part, subjects were blinded to study treatment; investigator was not blinded as this was not feasible due to the different nature of the 2 hemostatic treatments. Data from the Primary Part (II), including treatment assignment and accumulating efficacy data, were blinded from the sponsor.

Treatment group assignments were made using sealed blinded randomization envelopes, only opened upon identification of the TBS.

Arms

Are arms mutually exclusive?	Yes
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	FS 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
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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
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No investigational medicinal product assigned in this arm

Arm title	Preliminary Part I - FS Grifols
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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.

Arm type	Experimental
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Investigational medicinal product name	FS Grifols
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Solution for sealant
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Routes of administration	Topical use
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Dosage and administration details:

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

Number of subjects in period 1	Primary Part II - FS Grifols	Primary Part II - Manual Compression	Preliminary Part I - FS Grifols
Started	109	57	59
Completed	106	56	58
Not completed	3	1	1
Adverse event, serious fatal	2	-	1
Consent withdrawn by subject	1	-	-
Lost to follow-up	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Primary Part II - FS Grifols
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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
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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 title	Preliminary Part I - FS Grifols
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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.

Reporting group values	Primary Part II - FS Grifols	Primary Part II - Manual Compression	Preliminary Part I - FS Grifols
Number of subjects	109	57	59
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)	58	32	32
From 65-84 years	51	25	27
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	63.72	62.04	63.53
standard deviation	± 8.908	± 10.734	± 9.343
Gender categorical			
Units: Subjects			
Female	33	26	18
Male	76	31	41

Reporting group values	Total		
Number of subjects	225		
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)	122		
From 65-84 years	103		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	77		
Male	148		

End points

End points reporting groups

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 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.	
Subject analysis set title	Preliminary Part (I) - FS Grifols (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: For the Preliminary Part (I) of the study, the intent-to-treat (ITT) analysis set was defined as all subjects who met the intra-operative inclusion criterion and whom the investigator therefore intended to treat with FS Grifols.	
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 randomized to FS Grifols or MC.	
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 randomized to FS Grifols or MC.	
Subject analysis set title	Preliminary Part (I) - FS Grifols (PP)
Subject analysis set type	Per protocol
Subject analysis set description: The PP population included all subjects in the ITT population excluding any subject for whom there was at least 1 major protocol deviation that might have an impact on the primary efficacy assessment. The major protocol deviations were determined at a data review meeting and were documented in a data review report prior to the database lock.	
Subject analysis set title	Primary Part (II) - FS Grifols (PP)
Subject analysis set type	Per protocol
Subject analysis set description: The PP population included all subjects in the ITT population excluding any subject for whom there was at least 1 major protocol deviation that might have an impact on the primary efficacy assessment. The major protocol deviations were determined at a data review meeting and were documented in a data review report prior to the database lock.	
Subject analysis set title	Primary Part (II) - Manual Compression (PP)
Subject analysis set type	Per protocol
Subject analysis set description: The PP population included all subjects in the ITT population excluding any subject for whom there was at least 1 major protocol deviation that might have an impact on the primary efficacy assessment. The major protocol deviations were determined at a data review meeting and were documented in a data review report prior to the database lock.	

Primary: Proportion of subjects achieving hemostasis at the TBS by T4

End point title	Proportion of subjects achieving hemostasis at the TBS by T4
End point description: Proportion of subjects enrolled into the Primary Part (II) achieving hemostasis (Yes/No) at the target bleeding site (TBS) by T4 without occurrence of re-bleeding and reapplication of study treatment after T4 and until TClosure and without brisk bleeding and use of alternative hemostatic treatment after TStart and until TClosure.	
End point type	Primary
End point timeframe: From the start of treatment application (Tstart) at the TBS to the achievement of hemostasis at that site by T4	

End point values	Primary Part (II) - FS Grifols (ITT)	Primary Part (II) - Manual Compression (ITT)	Primary Part (II) - FS Grifols (PP)	Primary Part (II) - Manual Compression (PP)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	109	57	97	52
Units: percent				
number (not applicable)	76.1	22.8	77.3	23.1

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	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	3.339
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.047
upper limit	5.445

Statistical analysis title	Primary efficacy endpoint analysis (PP)
Comparison groups	Primary Part (II) - FS Grifols (PP) v Primary Part (II) - Manual Compression (PP) v Primary Part (II) - FS Grifols (ITT) v Primary Part (II) - Manual Compression (ITT)

Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	3.351
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.016
upper limit	5.567

Secondary: Time to Hemostasis (TTH)

End point title	Time to Hemostasis (TTH)
End point description:	
<p>The TTH was measured from TStart at the TBS. The precise TTH was not observable in this study. However, if hemostasis was not achieved at an assessment time point but was achieved at the next time point, it could be inferred that the true TTH was between those 2 assessment time points. Therefore, TTH, although not observed directly, was ascertained as falling into the following hemostatic time categories (HTCs):</p> <p>≤4 minutes from TStart to hemostasis (HTC ≤4).</p> <p>>4 minutes to ≤5 minutes from TStart to hemostasis (HTC >4 to ≤5).</p> <p>>5 minutes to ≤7 minutes from TStart to hemostasis (HTC >5 to ≤7).</p> <p>>7 minutes to ≤10 minutes from TStart to hemostasis (HTC >7 to ≤10).</p> <p>In addition, 1 non-hemostatic time category (NHTC) was defined:</p> <ul style="list-style-type: none"> • Persistent bleeding at TBS beyond 10-minute observational period (more than 10 minutes from TStart) (NHTC >10) 	
End point type	Secondary
End point timeframe:	
The TTH would be the time passed from TStart to that last effective hemostatic time point.	

End point values	Primary Part (II) - FS Grifols (ITT)	Primary Part (II) - Manual Compression (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	57		
Units: minutes				
arithmetic mean (standard error)	5.1 (± 0.21)	8.2 (± 0.35)		

Statistical analyses

Statistical analysis title	Analysis of TTH at TBS (ITT)
Comparison groups	Primary Part (II) - FS Grifols (ITT) v Primary Part (II) - Manual Compression (ITT)

Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank

Secondary: Cumulative proportion of subjects achieving hemostasis at the TBS by T5, T7, and T10

End point title	Cumulative proportion of subjects achieving hemostasis at the TBS by T5, T7, and T10
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End point description:

Cumulative proportion of subjects having achieved hemostasis at the TBS by each of the following Hemostatic Time Categories (HTCs): T5, T7 and T10

End point type	Secondary
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End point timeframe:

From the start of treatment application (Tstart) at the 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	Primary Part (II) - FS Grifols (ITT)	Primary Part (II) - Manual Compression (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	57		
Units: percent				
number (not applicable)				
Hemostasis by 5 minutes	80.7	28.1		
Hemostasis by 7 minutes	84.4	35.1		
Hemostasis by 10 minutes	88.1	45.6		

Statistical analyses

Statistical analysis title	Analysis of Hemostasis by T5, T7, and T10 at TBS
Comparison groups	Primary Part (II) - FS Grifols (ITT) v Primary Part (II) - Manual Compression (ITT)
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[1]
Method	Fisher exact

Notes:

[1] -	RR (95% CI)	P-value
Hemostasis by 5 min	2.876 (1.879, 4.402)	<0.001
Hemostasis by 7 min	2.406 (1.675, 3.455)	<0.001
Hemostasis by 10 min	1.931 (1.442, 2.585)	<0.001

Secondary: Prevalence of treatment failures

End point title	Prevalence of treatment failures
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End point description:

The following cases were considered treatment failures:

- Persistent bleeding at the TBS beyond T4.
- The event of breakthrough (brisk and forceful) bleeding from the TBS that jeopardized subject safety according to the investigator's judgment at any moment during the 10 minute observational period and until TClosure.
- Re-bleeding at the TBS after the assessment of the primary efficacy endpoint at T4 and until TClosure.
- Use of alternative hemostatic treatments or maneuvers (other than the study treatment) at the TBS during the 10-minute observational period and until TClosure or use of study treatment at the TBS beyond T4 and until TClosure.

Note: The reasons were not mutually exclusive

End point type	Secondary
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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	Primary Part (II) - FS Grifols (ITT)	Primary Part (II) - Manual Compression (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	57		
Units: percent				
number (not applicable)				
Persistent bleeding	22.9	77.2		
Breakthrough bleeding	3.7	3.5		
Re-bleeding	0.9	5.3		
Use of alternative hemostatic treatment or maneuvre	1.8	10.5		
Re-applied treatment	0	42.1		
Treatment failures, total	23.9	77.2		

Statistical analyses

Statistical analysis title	Analysis of Treatment Failure at TBS
Comparison groups	Primary Part (II) - Manual Compression (ITT) v Primary Part (II) - FS Grifols (ITT)
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	0.309

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.215
upper limit	0.445

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Subjects were monitored from the time of the signature of the ICF to Post-Operative Week 6 \pm 4 days for assessment of AEs.

Adverse event reporting additional description:

AEs were classified as treatment-emergent AEs (TEAEs) or non-treatment-emergent AEs (non-TEAEs) depending on the comparison of AE onset date/time with the start of study treatment. A TEAE was defined as an AE which occurred on or after the start of study treatment up to and including the date of the Week 6 Visit.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

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

Reporting group title	Manual compression [Primary Part (II)]
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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	34 / 168 (20.24%)	11 / 57 (19.30%)	
number of deaths (all causes)	4	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			

subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphorrhoea			
subjects affected / exposed	1 / 168 (0.60%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	2 / 168 (1.19%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
multi-organ failure			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 168 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	0 / 168 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (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			
Acute respiratory failure			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 168 (1.19%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 168 (1.19%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Subdural haematoma			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parvovirus B19 test positive			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reocclusion			
subjects affected / exposed	2 / 168 (1.19%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft occlusion			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			

subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 168 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 168 (1.19%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid sinus syndrome			
subjects affected / exposed	0 / 168 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			

subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diabetic gastroparesis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (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	2 / 168 (1.19%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (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			
Renal Failure acute			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (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			
Osteonecrosis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	2 / 168 (1.19%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 168 (0.60%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft infection			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (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	3 / 168 (1.79%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	3 / 168 (1.79%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 168 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	2 / 168 (1.19%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft thrombosis			
subjects affected / exposed	1 / 168 (0.60%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 57 (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	136 / 168 (80.95%)	44 / 57 (77.19%)	
Investigations			
Body temperature increased			

subjects affected / exposed occurrences (all)	10 / 168 (5.95%) 10	4 / 57 (7.02%) 4	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	9 / 168 (5.36%)	2 / 57 (3.51%)	
occurrences (all)	10	2	
Procedural pain			
subjects affected / exposed	58 / 168 (34.52%)	21 / 57 (36.84%)	
occurrences (all)	60	22	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 168 (1.19%)	3 / 57 (5.26%)	
occurrences (all)	2	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 168 (5.95%)	2 / 57 (3.51%)	
occurrences (all)	10	2	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	13 / 168 (7.74%)	1 / 57 (1.75%)	
occurrences (all)	15	1	
Pyrexia			
subjects affected / exposed	19 / 168 (11.31%)	6 / 57 (10.53%)	
occurrences (all)	21	6	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	7 / 168 (4.17%)	4 / 57 (7.02%)	
occurrences (all)	7	4	
Nausea			
subjects affected / exposed	10 / 168 (5.95%)	2 / 57 (3.51%)	
occurrences (all)	10	2	
Vomiting			
subjects affected / exposed	4 / 168 (2.38%)	3 / 57 (5.26%)	
occurrences (all)	4	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2012	<p>Protocol Version 1.1 was approved on 11 Jun 2012 and applied to all study centers in the US. Major changes included:</p> <ul style="list-style-type: none">- Removing age restriction of ≥ 3 years old to comply with PREA Requirements- Removing weight restriction of < 20 kg- Excluding mild bleeding subjects from Preliminary Part (I). In addition, the inclusion criteria referring to the type of bleeding for both parts of the study aligned so that only subjects with moderate bleeding intensity are enrolled- Adjusting the assumed screen failure rates in Preliminary Part (I)- Adjusting sample size calculations based on new reference data- Adjusting drop-out rate assumptions based on the lesser likelihood of subject withdrawal during the short intra-operative period- Excluding subjects with previous known sensitivity to heparin or protamine components to reduce the risk for the safety of the participating subjects- Addition of exclusion criteria #10 for subjects with recent surgical procedures to reduce risk for subjects & confounding factors for safety evaluation- Polymerization time (vessel clamping period) increased from 1 to 2 min in accordance with new reference data- Clarification that FS Grifols application at sites other than the TBS is disallowed- 3-min timepoint after start of treatment application was removed due to the extension of polymerization time to 2 min- Removing the IO vital sign measurements at 3 & 7 min- Addition of the time point of TEnd2 for documentation of the actual end time of FS Grifols reapplication- Addition of the procedure for sponsor evaluation and unblinding of reportable cases from the blinded part of the study (Primary Part [II])- Reducing pediatric blood sampling requirements for the safety of subjects < 30 kg
24 October 2012	<p>Protocol Version 1.2 was approved on 24 Oct 2012 and applied to all study centers in the US.</p> <p>Major changes included:</p> <ul style="list-style-type: none">• Addition of TStart2 time point due to the FDA's request to capture times of study drug reapplication, if applicable.

23 August 2013	<p>Protocol Version 2.0 was approved on 23 Aug 2013 and applied to all study centers in the US. Major changes included:</p> <ul style="list-style-type: none"> - Overall study duration increased from 17 to 48 total months - Clarification that subjects must have Hgb ≥ 9 g/dL at baseline within 24 hours prior to the surgical procedure - Clarification that females who were pregnant or nursing a child at baseline (within 24 hours prior to the surgical procedure) were excluded from the study. Laboratory testing for determination of the subject's eligibility was to be performed locally at the site - Expanded the list of acceptable surgical procedures to include testing of FS Grifols in bypass grafting at additional anatomic locations with larger vessels - Removing exclusion criterion #6 (Known [documented] previous exposure to thrombin-containing [bovine, human or recombinant] products) to allow testing of FS Grifols in subjects who were previously exposed to other thrombin products - Clarification for Day 0 recording of vital signs at 2, 4, & 6 hours after TCompletion - Clarification that the maximum total volume of FS Grifols allowed to be applied at the TBS would be approximately 12 mL (equivalent to the full content of 2 FS Grifols kits) - Reducing the number of Post-Operative Visits by removing visits on Post-Operative Days 1 & 3 - Shifting the following procedures from Post-Operative Days 1 and 3 to Post-Operative Day 2: coagulation panel (INR and aPTT ratio), CBC, and serum clinical chemistry -Clarification of laboratory panels for pediatric sampling.
16 January 2014	<p>Protocol Version 3.0 was approved on 16 Jan 2014 The key update to this protocol amendment was the addition of approximately 6 study centers in 2 new countries, Hungary and Serbia. An additional major change included:</p> <ul style="list-style-type: none"> • Removing the Month 6 Visit for virus safety testing after study drug administration. Removing the Month 6 Visit shortened the observation period from 6 months to 3 months and also shortened the subject's expected length of participation period from 7 months to 4 months.
25 March 2014	<p>Protocol Version 3.1 was approved on 25 Mar 2014 and applied to all study centers in Hungary. This country-specific protocol amendment was implemented to include the exclusion criterion (listed below) required by Hungary's national competent authority.</p> <ul style="list-style-type: none"> • Have known (documented) history of thrombophilia. • Have known (documented) history of IgA deficiency.
16 December 2014	<p>Protocol Version 4.0 and Version 4.1 were approved on 16 Dec 2014. The key update to Protocol Version 4.0 was the addition of approximately 6 study centers in 1 new country, Russia. Version 4.1 applied to all study centers in Hungary. The major changes included:</p> <ul style="list-style-type: none"> - Decreasing the Hgb levels criterion from ≥ 9.0 g/dL to ≥ 8.0 g/dL at baseline (within 24 hours prior to surgical procedure) to allow the enrollment of subjects with lower Hgb levels (eg, subjects receiving chemotherapy prior to surgery or pediatric subjects) that otherwise would be screening failures. Laboratory testing for determination of subject's eligibility was performed locally at the investigative study center. - Updating the FS Grifols shelf-life from 1 year to 2 years when stored at a temperature of $\leq -18^{\circ}\text{C}$ ($\leq -0.40^{\circ}\text{F}$). - Clarification that baseline central laboratory samples could be drawn shortly after anesthesia, but before the start of surgery.
31 March 2015	<p>Protocol Version 4.2 was approved on 31 Mar 2015 and applied to all study centers in Russia. The major changed included:</p> <ul style="list-style-type: none"> • Removal of pediatric subjects in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported