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 Soft Tissue Open Surgeries

Summary

EudraCT number	2013-005159-34
Trial protocol	HU
Global end of trial date	04 June 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	IG1103

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01731938
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Instituto Grifols, S.A
Sponsor organisation address	Can Guasch, 2, Parets del Valles, Barcelona, 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)	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	28 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 June 2015
Global end of trial reached?	Yes
Global end of trial date	04 June 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 soft tissue surgery

Protection of trial subjects:

For each investigative site, the Primary Part (II) started only after the enrollment of 4 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 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 Surgicel, 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: -

Evidence for comparator: -

Actual start date of recruitment	19 November 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	Serbia: 78
Country: Number of subjects enrolled	Hungary: 45
Country: Number of subjects enrolled	United States: 204
Worldwide total number of subjects	327
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)	11
Children (2-11 years)	5
Adolescents (12-17 years)	2
Adults (18-64 years)	243
From 65 to 84 years	61
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Study Initiation Date: 19 Nov 2012; Study Completion Date: 04 Jun 2015

Subjects were recruited from Hungary, Serbia and USA.

Pre-assignment

Screening details:

A total of 498 subjects were screened in this study. Of these, 327 subjects were randomized and 171 were screen failures.

Pre-assignment period milestones

Number of subjects started	498[1]
Number of subjects completed	327

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 13
Reason: Number of subjects	Lost to follow up: 5
Reason: Number of subjects	Physician decision: 4
Reason: Number of subjects	Protocol deviation: 1
Reason: Number of subjects	Inclusion/exclusion criteria not met: 118
Reason: Number of subjects	Others: 30

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: 171 patients are screen failed and hence not enrolled.

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 both parts of the study, subjects were blinded to their 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, except for personnel from study drug supply groups.
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	Preliminary Part I - FS Grifols

Arm description:

Subjects in the Preliminary Part (I) were to be randomized in 1:1 ratio into 1 of 2 treatment groups: FS Grifols or Surgicel. The main objective of this part of the clinical study was to ensure that local study teams familiarized themselves with the technique for FS Grifols application and with intra-operative procedures required by the protocol of the clinical study.

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 or spray applicator tip at the target bleeding site (TBS)

Arm title	Preliminary Part I - Surgicel

Arm description:

Subjects in the Preliminary Part (I) were to be randomized in 1:1 ratio into 1 of 2 treatment groups: FS Grifols or Surgicel. The main objective of this part of the clinical study was to ensure that local study teams familiarized themselves with the technique for FS Grifols application and with intra-operative procedures required by the protocol of the clinical study.

Arm type	Medical device
Investigational medicinal product name	Surgicel (regenerated oxidized cellulose)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sealant matrix
Routes of administration	Topical use

Dosage and administration details:

Up to four (4) 4" x 8" sheets of Surgicel

Arm title	Primary Part II - FS Grifols

Arm description:

Subjects in the Primary (II) Part of the study were randomly allocated into one of two treatment groups: FS Grifols or Surgicel. This part of the clinical trial had two main objectives:
1. assessment of the efficacy of FS Grifols
2. assessment of safety of FS Grifols

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 or spray applicator tip at the target bleeding site (TBS)

Arm title	Primary Part II - Surgicel

Arm description:

Subjects in the Primary (II) Part of the study were randomly allocated into one of two treatment groups: FS Grifols or Surgicel. This part of the clinical trial had two main objectives:
1. assessment of the efficacy of FS Grifols
2. assessment of safety of FS Grifols

Arm type	Medical device
Investigational medicinal product name	Surgicel (regenerated oxidized cellulose)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sealant matrix
Routes of administration	Topical use

Dosage and administration details:

Up to four (4) 4" x 8" sheets of Surgicel

Number of subjects in period 1	Preliminary Part I - FS Grifols	Preliminary Part I - Surgicel	Primary Part II - FS Grifols
Started	51	52	116
Completed	48	44	103
Not completed	3	8	13
Adverse event, serious fatal	-	-	2
Physician decision	1	-	-
Consent withdrawn by subject	2	2	5
Others	-	3	-
any other	-	-	-
other(s)	-	-	2
Lost to follow-up	-	3	4

Number of subjects in period 1	Primary Part II - Surgicel
Started	108
Completed	95
Not completed	13
Adverse event, serious fatal	1
Physician decision	-
Consent withdrawn by subject	4
Others	-
any other	3
other(s)	-
Lost to follow-up	5

Baseline characteristics

Reporting groups	
Reporting group title	Preliminary Part I - FS Grifols
Reporting group description:	
Subjects in the Preliminary Part (I) were to be randomized in 1:1 ratio into 1 of 2 treatment groups: FS Grifols or Surgicel. The main objective of this part of the clinical study was to ensure that local study teams familiarized themselves with the technique for FS Grifols application and with intra-operative procedures required by the protocol of the clinical study.	
Reporting group title	Preliminary Part I - Surgicel
Reporting group description:	
Subjects in the Preliminary Part (I) were to be randomized in 1:1 ratio into 1 of 2 treatment groups: FS Grifols or Surgicel. The main objective of this part of the clinical study was to ensure that local study teams familiarized themselves with the technique for FS Grifols application and with intra-operative procedures required by the protocol of the clinical study.	
Reporting group title	Primary Part II - FS Grifols
Reporting group description:	
Subjects in the Primary (II) Part of the study were randomly allocated into one of two treatment groups: FS Grifols or Surgicel. This part of the clinical trial had two main objectives: 1. assessment of the efficacy of FS Grifols 2. assessment of safety of FS Grifols	
Reporting group title	Primary Part II - Surgicel
Reporting group description:	
Subjects in the Primary (II) Part of the study were randomly allocated into one of two treatment groups: FS Grifols or Surgicel. This part of the clinical trial had two main objectives: 1. assessment of the efficacy of FS Grifols 2. assessment of safety of FS Grifols	

Reporting group values	Preliminary Part I - FS Grifols	Preliminary Part I - Surgicel	Primary Part II - FS Grifols
Number of subjects	51	52	116
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)	5	6	0
Children (2-11 years)	3	2	0
Adolescents (12-17 years)	0	1	1
Adults (18-64 years)	27	28	98
From 65-84 years	13	14	16
85 years and over	3	1	1
Age continuous Units: years			
arithmetic mean	47.17	45.39	48.51
standard deviation	± 25.635	± 25.024	± 14.369
Gender categorical Units: Subjects			
Female	27	28	87
Male	24	24	29

Reporting group values	Primary Part II -	Total	

	Surgicel		
Number of subjects	108	327	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	11	
Children (2-11 years)	0	5	
Adolescents (12-17 years)	0	2	
Adults (18-64 years)	90	243	
From 65-84 years	18	61	
85 years and over	0	5	
Age continuous Units: years			
arithmetic mean	46.72		
standard deviation	± 14.33	-	
Gender categorical Units: Subjects			
Female	86	228	
Male	22	99	

End points

End points reporting groups

Reporting group title	Preliminary Part I - FS Grifols
Reporting group description:	
Subjects in the Preliminary Part (I) were to be randomized in 1:1 ratio into 1 of 2 treatment groups: FS Grifols or Surgicel. The main objective of this part of the clinical study was to ensure that local study teams familiarized themselves with the technique for FS Grifols application and with intra-operative procedures required by the protocol of the clinical study.	
Reporting group title	Preliminary Part I - Surgicel
Reporting group description:	
Subjects in the Preliminary Part (I) were to be randomized in 1:1 ratio into 1 of 2 treatment groups: FS Grifols or Surgicel. The main objective of this part of the clinical study was to ensure that local study teams familiarized themselves with the technique for FS Grifols application and with intra-operative procedures required by the protocol of the clinical study.	
Reporting group title	Primary Part II - FS Grifols
Reporting group description:	
Subjects in the Primary (II) Part of the study were randomly allocated into one of two treatment groups: FS Grifols or Surgicel. This part of the clinical trial had two main objectives: 1. assessment of the efficacy of FS Grifols 2. assessment of safety of FS Grifols	
Reporting group title	Primary Part II - Surgicel
Reporting group description:	
Subjects in the Primary (II) Part of the study were randomly allocated into one of two treatment groups: FS Grifols or Surgicel. This part of the clinical trial had two main objectives: 1. assessment of the efficacy of FS Grifols 2. assessment of 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:	
In the Preliminary Part (I), the intent-to-treat (ITT) analysis set was defined as all subjects randomized to FS Grifols.	
Subject analysis set title	Preliminary Part (I) - Surgicel (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 as all subjects randomized to Surgicel.	
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), the intent-to-treat (ITT) analysis set was defined as all subjects randomized to FS Grifols.	
Subject analysis set title	Primary Part (II) - Surgicel (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
In the Primary Part (II), the intent-to-treat (ITT) analysis set was defined as all subjects randomized to Surgicel.	
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 included all subjects in the ITT population excluding any subject for whom there was at least one 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	Preliminary Part (I) - Surgicel (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population included all subjects in the ITT population excluding any subject for whom there was at least one 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 per protocol (PP) population included all subjects in the ITT population excluding any subject for whom there was at least one 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) - Surgicel (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population included all subjects in the ITT population excluding any subject for whom there was at least one 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 four (4) minutes

End point title	Proportion of subjects achieving hemostasis at the TBS by four (4) minutes

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) - Surgicel (ITT)	Primary Part (II) - FS Grifols (PP)	Primary Part (II) - Surgicel (PP)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	116	108	104	102
Units: percent				
number (not applicable)	82.8	77.8	83.7	76.5

Statistical analyses

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

Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.401
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1.064
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.934
upper limit	1.213

Notes:

[1] - Primary efficacy endpoint

Statistical analysis title	Primary efficacy endpoint analysis (PP)
Comparison groups	Primary Part (II) - FS Grifols (PP) v Primary Part (II) - Surgicel (PP)
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.224
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1.094
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.954
upper limit	1.255

Secondary: Cumulative proportion of subjects achieving hemostasis at TBS by T3

End point title	Cumulative proportion of subjects achieving hemostasis at TBS by T3

End point description:

The cumulative proportion of subjects achieving hemostasis at the TBS by T3 was defined as an absence/cessation of bleeding at the TBS by that time point without occurrence of re-bleeding, brisk bleeding, use of alternative hemostatic treatment, and reapplication of study treatment after T4 and until TClosure.

End point type	Secondary

End point timeframe:

From the start of treatment application (Tstart) at the TBS to achievement of hemostasis at that site by T3.

End point values	Primary Part (II) - FS Grifols (ITT)	Primary Part (II) - Surgicel (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	108		
Units: percent				
number (not applicable)	75.9	60.2		

Statistical analyses

Statistical analysis title	Secondary efficacy analysis of hemostasis by T3

Statistical analysis description:

The ratio of proportion of subjects meeting the efficacy endpoint in the two treatment groups in Primary Part II.

Comparison groups	Primary Part (II) - FS Grifols (ITT) v Primary Part (II) - Surgicel (ITT)
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.015
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.048
upper limit	1.516

Secondary: Time to Hemostasis (TTH)

End point title	Time to Hemostasis (TTH)

End point description:

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):

≤2 minutes from TStart to hemostasis (HTC ≤2).
>2 minutes to ≤3 minutes from TStart to hemostasis (HTC >2 to ≤3).
>3 minutes to ≤4 minutes from TStart to hemostasis (HTC >3 to ≤4).
>4 minutes to ≤5 minutes from TStart to hemostasis (HTC >4 to ≤5).
>5 minutes to ≤7 minutes from TStart to hemostasis (HTC >5 to ≤7).
>7 minutes to ≤10 minutes from TStart to hemostasis (HTC >7 to ≤10).

In addition, 1 non-hemostatic time category (NHTC) was defined:
- 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) - Surgicel (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	108		
Units: minutes				
arithmetic mean (standard error)	3.6 (± 0.25)	4.2 (± 0.29)		

Statistical analyses

Statistical analysis title	Analysis of TTH at TBS (ITT)
Comparison groups	Primary Part (II) - FS Grifols (ITT) v Primary Part (II) - Surgicel (ITT)
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.06
Method	Logrank

Secondary: Cumulative proportion of subjects achieving hemostasis at TBS by T2, T5, T7, and T10

End point title	Cumulative proportion of subjects achieving hemostasis at TBS by T2, T5, T7, and T10

End point description:

End point type	Secondary

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) - Surgicel (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	108		
Units: percent				
number (not applicable)				
Hemostasis by 2 minutes	53.4	43.5		
Hemostasis by 5 minutes	83.6	78.7		
Hemostasis by 7 minutes	86.2	81.5		
Hemostasis by 10 minutes	89.7	83.3		

Statistical analyses

Statistical analysis title	Secondary efficacy analysis
Comparison groups	Primary Part (II) - FS Grifols (ITT) v Primary Part (II) - Surgicel (ITT)
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.144 [2]
Method	Fisher exact

Notes:

[2] - Hemostasis by 2 minutes: p= 0.144
Hemostasis by 5 minutes: p= 0.394
Hemostasis by 7 minutes: p= 0.367
Hemostasis by 10 minutes: p= 0.176

Secondary: Prevalence of treatment failures

End point title	Prevalence of treatment failures

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

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) - Surgicel (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	116	108		
Units: percent				
number (not applicable)				
Persistent bleeding	13.8	21.3		
Breakthrough bleeding	2.6	2.8		
Re-bleeding	4.3	2.8		
Use of alternative hemostatic treatment or maneuve	7.8	16.7		
Re-applied treatment	1.7	0		

Treatment failures, total	17.2	22.2		

Statistical analyses

Statistical analysis title	Prevalence of treatment failures
Comparison groups	Primary Part (II) - FS Grifols (ITT) v Primary Part (II) - Surgicel (ITT)
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.401
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	0.776
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.456
upper limit	1.321

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

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.

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

Reporting group description: -

Serious adverse events	FS Grifols [pooled Preliminary Part (I) + Primary Part (II)]	Surgicel [pooled Preliminary Part (I) + Primary Part (II)]	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 169 (10.06%)	18 / 158 (11.39%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			
subjects affected / exposed	1 / 169 (0.59%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	2 / 169 (1.18%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic complication			
subjects affected / exposed	0 / 169 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic leak			

subjects affected / exposed	1 / 169 (0.59%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 169 (0.59%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus			
subjects affected / exposed	2 / 169 (1.18%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	1 / 169 (0.59%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 169 (0.59%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 169 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound evisceration			
subjects affected / exposed	1 / 169 (0.59%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound secretion			
subjects affected / exposed	0 / 169 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 169 (0.59%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 169 (0.59%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 169 (0.59%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 169 (0.59%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 169 (0.59%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 169 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	1 / 169 (0.59%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	2 / 169 (1.18%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	2 / 169 (1.18%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 169 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 169 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 169 (0.59%)	0 / 158 (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 / 169 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 169 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hydrothorax			
subjects affected / exposed	0 / 169 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			

subjects affected / exposed	0 / 169 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngospasm			
subjects affected / exposed	1 / 169 (0.59%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 169 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 169 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 169 (1.18%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 169 (0.00%)	1 / 158 (0.63%)	
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 acute			
subjects affected / exposed	1 / 169 (0.59%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 169 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Clostridium difficile colitis			
subjects affected / exposed	0 / 169 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	0 / 169 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 169 (0.59%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 169 (0.59%)	0 / 158 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 169 (0.00%)	3 / 158 (1.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal abscess			
subjects affected / exposed	0 / 169 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 169 (0.59%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 169 (0.00%)	1 / 158 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	0 / 169 (0.00%)	2 / 158 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 169 (0.59%)	0 / 158 (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)]	Surgicel [pooled Preliminary Part (I) + Primary Part (II)]	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	149 / 169 (88.17%)	139 / 158 (87.97%)	
Injury, poisoning and procedural complications			
Incision site pain			
subjects affected / exposed	9 / 169 (5.33%)	7 / 158 (4.43%)	
occurrences (all)	9	7	
Procedural nausea			
subjects affected / exposed	24 / 169 (14.20%)	31 / 158 (19.62%)	
occurrences (all)	25	31	
Procedural pain			
subjects affected / exposed	92 / 169 (54.44%)	86 / 158 (54.43%)	
occurrences (all)	95	86	
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 169 (7.69%)	12 / 158 (7.59%)	
occurrences (all)	13	12	
Hypotension			
subjects affected / exposed	11 / 169 (6.51%)	5 / 158 (3.16%)	
occurrences (all)	11	5	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 169 (7.10%)	14 / 158 (8.86%)	
occurrences (all)	12	15	
General disorders and administration			

site conditions Pyrexia subjects affected / exposed occurrences (all)	 12 / 169 (7.10%) 12	 15 / 158 (9.49%) 16	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 19 / 169 (11.24%) 19 23 / 169 (13.61%) 27 12 / 169 (7.10%) 13	 11 / 158 (6.96%) 11 18 / 158 (11.39%) 19 9 / 158 (5.70%) 10	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	 9 / 169 (5.33%) 9	 10 / 158 (6.33%) 10	
Infections and infestations Cervicitis subjects affected / exposed occurrences (all)	 9 / 169 (5.33%) 9	 6 / 158 (3.80%) 6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2012	Protocol Version 2.0 was approved on 16 Jul 2012 and applied to all study centers in the US. Major changes included: - Removing age restriction of ≥3 years old to comply with Pediatric Research Equity Act Requirements. - Removing the weight restriction of <20 kg. - Modifying the Preliminary Part (I) of the study to randomize subjects into the FS Grifols or Surgicel treatment groups, providing the investigators an opportunity to become familiar with using the FS Grifols and Surgicel products in a variety of bleed types and to also generate data to corroborate the Primary Part (II) effect size assumptions. - Excluding mild bleeding subjects from the Preliminary Part (I) of the study to further increase the relevance of the experience gained in the Preliminary Part (I). In addition, the exclusion aligned the study to the intra-operative inclusion criteria of a TBS with moderate bleeding intensity. - Adjusting sample size calculations due to the change in the randomization ratio from 2:1 to 1:1 to FS Grifols or Surgicel treatment groups. - Disallowing FS Grifols and Surgicel application after the primary endpoint assessment (T4) or at sites other than the TBS to reduce/minimize confounding factors in the assessment of efficacy and safety. - Reducing intraoperative vital signs measurements to alleviate the number of procedures performed in a short period without adding substantial benefit in terms of safety monitoring. - Adding a procedure for handling missing data for the primary efficacy endpoint. Missing hemostatic assessment would be treated as a failure or as not achieving hemostasis at TBS at T4. - Adding sensitivity analysis adjusted for the study center. - Addition of the testing method and multiplicity adjustment for secondary efficacy endpoints. - Adjusting blood sampling requirements for pediatric subjects <30 kg by eliminating the virology Follow-Up Visits.
24 October 2012	Protocol Version 2.1 was approved on 24 Oct 2012 and applied to all study centers in the US. The major change included: Addition of TStart2 and TEnd2 time points due to the FDA’s request to capture times of study drug reapplication, if applicable.

23 August 2013	Protocol Version 3.0 was approved on 23Aug2013 and applied to all centers in the US. Major changes were: - Testing FS Grifols in additional soft tissue surgical types beyond retroperitoneal and pelvic regions, ie mastopexies and abdominoplasties. The % of subjects enrolled with mastopexies and abdominoplasties could not have been >35% in the Primary Part (II). Lymphadenectomies were permitted in the retroperitoneal or pelvic region, only. - Excluding subjects requiring thoracic & abdominal surgery due to trauma. - Clarification that pregnant females or nursing a child at baseline (within 24 hours prior to surgical procedure) were excluded from the study. Laboratory testing for determination of subject's eligibility was to be performed locally at the site. - Removing exclusion criterion #5 to allow testing of FS Grifols in subjects previously exposed to other thrombin products. The collection of safety information in those subjects would help determine safety profile of FS Grifols in a broader subject population. - Clarification that 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 number of Post-Operative Visits by removing visits on Post-Operative Days 1 & 3. - Shifting the following procedures from Post-Operative Days 1 & 3 to Post-Operative Day 2: coagulation panel (INR and aPTT ratio), CBC, and serum clinical chemistry. - Clarification of laboratory panels for pediatric sampling. In pediatric subjects weighing <30 kg, pediatric tubes must have been utilized for CBC, blood coagulation parameters, and serum clinical chemistry. Virology and immunogenicity sampling was eliminated. In pediatric subjects weighing ≥30 kg, pediatric or adult tubes could be utilized for CBC, blood coagulation parameters, and serum clinical chemistry. Virology and immunogenicity sampling may or may not have been performed according to the judgement of the investigator
16 January 2014	Protocol Version 4.0 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: - 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	Protocol Version 4.1 was approved on 25 Mar 2014 and applied only to study centers in Hungary. This country-specific protocol amendment was implemented to include the exclusion criteria (listed below) required by Hungary's national competent authority. - Have known (documented) history of thrombophilia. - Have known (documented) history of IgA deficiency.
16 December 2014	Protocol Version 5.0 and Version 5.1 were approved on 16 Dec 2014. Protocol Version 5.0 applied to all study centers in the US and Serbia; Version 5.1 applied to all study centers in Hungary. The major changes included: - Increasing the number of preliminary pediatric subjects from 15 to 24 to supplement pediatric population. - 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 ≤-18ºC (≤-0.40ºF). - Clarification that baseline central laboratory samples could be drawn shortly after anesthesia but before the start of surgery.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported