



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 Parenchymous Tissue Open Surgeries

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2013-005128-40 |
| Trial protocol | HU |
| Global end of trial date | 28 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 | IG1102 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01754480 |
| 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) | 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 | 04 May 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 December 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 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 parenchymous 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 | 22 March 2013 |
| 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: 103 |
| Country: Number of subjects enrolled | Russian Federation: 5 |
| Country: Number of subjects enrolled | United States: 179 |
| Country: Number of subjects enrolled | Hungary: 38 |
| Worldwide total number of subjects | 325 |
| EEA total number of subjects | 38 |

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) | 1 |
| Children (2-11 years) | 2 |
| Adolescents (12-17 years) | 2 |
| Adults (18-64 years) | 201 |
| From 65 to 84 years | 119 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Study Initiation Date: 22 March 2013; Study Completion Date: 28 Dec 2015

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

Pre-assignment

Screening details:

A total of 426 subjects were screened in this study. Of these, 325 subjects were randomized and 101 were screen failures.

Pre-assignment period milestones

| | |
|------------------------------|--------------------|
| Number of subjects started | 426 ^[1] |
| Number of subjects completed | 325 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|--|
| Reason: Number of subjects | Consent withdrawn by subject: 7 |
| Reason: Number of subjects | Physician decision: 11 |
| Reason: Number of subjects | Protocol deviation: 1 |
| Reason: Number of subjects | inclusion/exclusion criteria not met: 66 |
| Reason: Number of subjects | others: 16 |

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: 101 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 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 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 | 52 | 49 | 111 |
| Completed | 47 | 45 | 100 |
| Not completed | 5 | 4 | 11 |
| Adverse event, serious fatal | 3 | 1 | 4 |
| Consent withdrawn by subject | 1 | 2 | 2 |
| others | - | - | 1 |
| Lost to follow-up | 1 | 1 | 4 |

| Number of subjects in period 1 | Primary Part II - Surgicel |
|---------------------------------------|----------------------------|
| Started | 113 |
| Completed | 108 |
| Not completed | 5 |
| Adverse event, serious fatal | 1 |
| Consent withdrawn by subject | 4 |
| others | - |
| Lost to follow-up | - |

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 | 52 | 49 | 111 |
| 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 | 1 | 0 |
| Children (2-11 years) | 2 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 2 | 0 |
| Adults (18-64 years) | 30 | 25 | 70 |
| From 65-84 years | 20 | 21 | 41 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 56.58 | 55.49 | 59.87 |
| standard deviation | ± 16.464 | ± 18.249 | ± 12.222 |
| Gender categorical Units: Subjects | | | |
| Female | 26 | 27 | 52 |
| Male | 26 | 22 | 59 |

| | | | |
|------------------------|-------------------|-------|--|
| Reporting group values | Primary Part II - | Total | |
|------------------------|-------------------|-------|--|

Surgicel

| | | | |
|---|----------|-----|--|
| Number of subjects | 113 | 325 | |
| 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 | 1 | |
| Children (2-11 years) | 0 | 2 | |
| Adolescents (12-17 years) | 0 | 2 | |
| Adults (18-64 years) | 76 | 201 | |
| From 65-84 years | 37 | 119 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 57.71 | | |
| standard deviation | ± 13.595 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 50 | 155 | |
| Male | 63 | 170 | |

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 | 111 | 113 | 87 | 100 |
| Units: percent | | | | |
| number (not applicable) | 92.8 | 80.5 | 98.9 | 85 |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Primary efficacy endpoint analysis (ITT) |
| Statistical analysis description: | |
| Study 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. | |

| | |
|---|---|
| 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 | = 0.01 |
| Method | Fisher exact |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.152 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.038 |
| upper limit | 1.279 |

| | |
|---|---|
| Statistical analysis title | Primary efficacy endpoint analysis (PP) |
| Comparison groups | Primary Part (II) - Surgicel (PP) v Primary Part (II) - FS Grifols (PP) |
| Number of subjects included in analysis | 187 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | < 0.001 |
| Method | Fisher exact |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.163 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.068 |
| upper limit | 1.267 |

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

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|---|---|
| End point title | Cumulative proportion of subjects achieving hemostasis at the 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 | 111 | 113 | | |
| Units: percent | | | | |
| number (not applicable) | 85.6 | 62.8 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Secondary efficacy analysis of hemostasis by T3 |
| 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 | superiority |
| P-value | < 0.001 |
| Method | Fisher exact |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.362 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.16 |
| upper limit | 1.6 |

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>≤2 minutes from TStart to hemostasis (HTC ≤2).</p> <p>>2 minutes to ≤3 minutes from TStart to hemostasis (HTC >2 to ≤3).</p> <p>>3 minutes to ≤4 minutes from TStart to hemostasis (HTC >3 to ≤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> <p>Persistent bleeding at TBS beyond 10-minute observational period (more than 10 minutes from TStart) (NHTC >10)</p> | |
| 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 | 111 | 113 | | |
| Units: minutes | | | | |
| arithmetic mean (standard error) | 2.8 (\pm 0.14) | 3.8 (\pm 0.24) | | |

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 | superiority |
| P-value | < 0.001 |
| Method | Logrank |

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

| | |
|------------------------|---|
| End point title | Cumulative proportion of subjects achieving hemostasis at the TBS by T2, T5, T7, and T10 |
| End point description: | Cumulative proportion of subjects having achieved hemostasis at the TBS by each of the following Hemostatic Time Categories (HTCs): T2, T5, T7 and T10 |
| 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 | 111 | 113 | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Hemostasis by 2 minutes | 55.9 | 41.6 | | |
| Hemostasis by 5 minutes | 97.3 | 85 | | |
| Hemostasis by 7 minutes | 97.3 | 87.6 | | |
| Hemostasis by 10 minutes | 98.2 | 92 | | |

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 | superiority |
| P-value | = 0.045 ^[1] |
| Method | Fisher exact |

Notes:

[1] - Hemostasis by 2 minutes: p= 0.045

Hemostasis by 5 minutes: p= 0.002

Hemostasis by 7 minutes: p= 0.010

Hemostasis by 10 minutes: p= 0.059

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 | 111 | 113 | | |
| Units: percent | | | | |
| number (not applicable) | | | | |
| Persistent bleeding | 7.2 | 18.6 | | |
| Breakthrough bleeding | 0 | 0.9 | | |
| Re-bleeding | 0 | 3.5 | | |
| Use of alternative hemostatic treatment or maneuvre | 0.9 | 8 | | |
| Re-applied treatment | 0.9 | 0.9 | | |
| Treatment failures, total | 7.2 | 19.5 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Prevalence of treatment failures |
| Comparison groups | Primary Part (II) - Surgicel (ITT) v Primary Part (II) - FS Grifols (ITT) |
| Number of subjects included in analysis | 224 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.01 |
| Method | Fisher exact |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.172 |
| upper limit | 0.796 |

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 |
|-----------------|------------|

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:

Subjects from the Preliminary Part (I) and from the Primary Part (II) of the study treated with Surgicel have been pooled for summarizing safety data of the study.

| 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 | 30 / 163 (18.40%) | 23 / 162 (14.20%) | |
| number of deaths (all causes) | 7 | 3 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuroendocrine carcinoma | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 162 (0.62%) | |
| 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 | 3 / 163 (1.84%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 163 (1.23%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Lung operation | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (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 | | | |
| Device occlusion | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extravasation | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 4 / 163 (2.45%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 163 (1.84%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 3 / 163 (1.84%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Electrocardiogram ST segment abnormal | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (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 | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural bile leak | | | |
| subjects affected / exposed | 4 / 163 (2.45%) | 2 / 162 (1.23%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous injury | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 162 (0.62%) | |
| 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 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 163 (0.61%) | 2 / 162 (1.23%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (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 / 163 (0.61%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (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 | | | |
| Brain injury | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (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 | 0 / 163 (0.00%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic anaemia | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised intraabdominal fluid collection | | | |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 162 (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 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Biloma | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 2 / 163 (1.23%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic necrosis | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Ischaemic hepatitis | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (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 | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 3 / 163 (1.84%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 2 / 162 (1.23%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterovirus infection | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| liver abscess | | | |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| pneumonia | | | |
| subjects affected / exposed | 2 / 163 (1.23%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhinovirus infection | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 163 (1.23%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis syndrome | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 2 / 162 (1.23%) | |
| 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 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 163 (1.23%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Failure to thrive | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gout | | | |
| subjects affected / exposed | 0 / 163 (0.00%) | 1 / 162 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatremia | | | |
| subjects affected / exposed | 1 / 163 (0.61%) | 0 / 162 (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 | 134 / 163 (82.21%) | 139 / 162 (85.80%) | |
| Injury, poisoning and procedural complications | | | |
| Incision site pain | | | |
| subjects affected / exposed | 12 / 163 (7.36%) | 11 / 162 (6.79%) | |
| occurrences (all) | 12 | 11 | |
| Procedural haemorrhage | | | |
| subjects affected / exposed | 9 / 163 (5.52%) | 4 / 162 (2.47%) | |
| occurrences (all) | 9 | 4 | |
| Procedural pain | | | |

| | | | |
|---|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 59 / 163 (36.20%) 63 | 61 / 162 (37.65%) 66 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 14 / 163 (8.59%) | 12 / 162 (7.41%) | |
| occurrences (all) | 14 | 12 | |
| Hypotension | | | |
| subjects affected / exposed | 21 / 163 (12.88%) | 9 / 162 (5.56%) | |
| occurrences (all) | 22 | 10 | |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 14 / 163 (8.59%) | 24 / 162 (14.81%) | |
| occurrences (all) | 14 | 24 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 21 / 163 (12.88%) | 26 / 162 (16.05%) | |
| occurrences (all) | 21 | 26 | |
| General disorders and administration site conditions | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 14 / 163 (8.59%) | 11 / 162 (6.79%) | |
| occurrences (all) | 15 | 11 | |
| Pyrexia | | | |
| subjects affected / exposed | 16 / 163 (9.82%) | 19 / 162 (11.73%) | |
| occurrences (all) | 18 | 19 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 10 / 163 (6.13%) | 3 / 162 (1.85%) | |
| occurrences (all) | 10 | 3 | |
| Constipation | | | |
| subjects affected / exposed | 20 / 163 (12.27%) | 23 / 162 (14.20%) | |
| occurrences (all) | 20 | 23 | |
| Nausea | | | |
| subjects affected / exposed | 34 / 163 (20.86%) | 38 / 162 (23.46%) | |
| occurrences (all) | 37 | 39 | |
| Vomiting | | | |

| | | | |
|--|------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 13 / 163 (7.98%) 14 | 17 / 162 (10.49%) 17 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Atelectasis | | | |
| subjects affected / exposed | 11 / 163 (6.75%) | 10 / 162 (6.17%) | |
| occurrences (all) | 11 | 10 | |
| Dyspnoea | | | |
| subjects affected / exposed | 8 / 163 (4.91%) | 11 / 162 (6.79%) | |
| occurrences (all) | 8 | 12 | |
| Pleural effusion | | | |
| subjects affected / exposed | 11 / 163 (6.75%) | 9 / 162 (5.56%) | |
| occurrences (all) | 12 | 10 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 12 / 163 (7.36%) | 12 / 162 (7.41%) | |
| occurrences (all) | 12 | 12 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 6 / 163 (3.68%) | 11 / 162 (6.79%) | |
| occurrences (all) | 6 | 11 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 6 / 163 (3.68%) | 11 / 162 (6.79%) | |
| occurrences (all) | 6 | 11 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 8 / 163 (4.91%) | 15 / 162 (9.26%) | |
| occurrences (all) | 8 | 15 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 16 July 2012 | <p>Protocol Version 2.0 was approved on 16 Jul 2012 and applied to all study centers in the US.</p> <p>Major changes included:</p> <ul style="list-style-type: none">• 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 Surgical treatment groups.• Removing drip application of FS Grifols because the usage is unlikely for the designated surgery type.• 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 . |
| 24 October 2012 | <p>Protocol Version 2.1 was approved on 24 Oct 2012 and applied to all study centers in the US.</p> <p>The major change included:</p> <ul style="list-style-type: none">• Addition of TStart2 and TEnd2 time points due to the FDA's request to capture times of study drug re-application, if applicable. |

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| 23 August 2013 | <p>Protocol Version 3.0 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"> • Clarification that females who were pregnant 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 study center. • Removing exclusion criterion #5 (Known [documented] previous exposure to thrombincontaining [bovine, human or recombinant] products) to allow testing of FS Grifols in subjects who were previously exposed to other thrombin products. The collection of safety information in those subjects would help determine the safety profile of FS Grifols in a broader subject population. • 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). <p>Reducing the number of Post-Operative Visits by removing visits on Post-Operative Days 1 and 3.</p> <ul style="list-style-type: none"> • 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. 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 | <p>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. Major changes 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. • Clarification that concurrent interventions on the pancreas, gall bladder, bile duct, or intestines were allowed. |
| 25 March 2014 | <p>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.</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 5.0 and Version 5.1 were approved on 16 Dec 2014. The key update to these protocol amendments were the addition of approximately 2 study centers in a new country, Russia. Version 5.0 applied to study centers in the US and Serbia; Version 5.1 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 ≤-18°C (≤-0.40°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 5.2 was approved on 31 Mar 2015 and applied only to study centers in Russia. The major change included:</p> <ul style="list-style-type: none"> • Removal of pediatric subject participation in the study. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported