



Clinical trial results:

A Prospective, Randomised, Active-Controlled, Single-blind, Parallel Group Clinical Trial to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis during Surgery in Paediatric Subjects.

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2016-004489-24 |
| Trial protocol | BG HU DE FR SE GB RO |
| Global end of trial date | 20 May 2022 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 23 June 2023 |
| First version publication date | 15 December 2022 |
| Version creation reason | • Correction of full data set Minor changes required |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | IG1405 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03461406 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Instituto Grifols, S.A |
| Sponsor organisation address | Can Guasch, 2, Parets del Vallès, Barcelona, Spain, 08150 |
| Public contact | Department of Drug Development, Instituto Grifols, S.A., 34 935712000, IGregulatory.affairs@grifols.com |
| Scientific contact | Department of Drug Development, Instituto Grifols, S.A., 34 935712000, 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? | Yes |

Notes:

Results analysis stage

| | |
|--|-------------|
| Analysis stage | Final |
| Date of interim/final analysis | 20 May 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 20 May 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The objective of the study is to evaluate if FS Grifols is non-inferior to EVICEL® in terms of the percentage of subjects achieving hemostasis at the target bleeding site (TBS) by 4 minutes (T4) from the start of treatment application (TStart) with no occurrence of rebleeding until the completion of the surgical closure by layers of the exposed surgical field containing the TBS (TClosure).

Protection of trial subjects:

Written Informed Consent Form (ICF) by the subject or a parent and/or legal guardian along with subject assent were obtained before any study specific procedure took place.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 18 January 2019 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 28 |
| Country: Number of subjects enrolled | Bulgaria: 26 |
| Country: Number of subjects enrolled | France: 1 |
| Country: Number of subjects enrolled | Hungary: 21 |
| Country: Number of subjects enrolled | Romania: 62 |
| Country: Number of subjects enrolled | Serbia: 44 |
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Worldwide total number of subjects | 186 |
| EEA total number of subjects | 110 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 6 |
| Infants and toddlers (28 days-23 months) | 37 |

| | |
|---------------------------|----|
| Children (2-11 years) | 67 |
| Adolescents (12-17 years) | 76 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at sites in the United States, Bulgaria, France, Hungary, Romania, Serbia, and United Kingdom, from 18 January 2019 (first subject enrolled to receive the study drug) to 20 May 2022 (last subject completed).

Pre-assignment

Screening details:

Paediatric subjects with excessive bleeding during surgery were randomized into 1: 1 ratio to receive FS Grifols and EVICEL. A total of 197 subjects were screened, out of which 186 subjects were randomized (Intent-to-treat population), 178 received study treatment (modified intent-to-treat population), 171 subjects completed the study.

Period 1

| | |
|------------------------------|---------------------------------|
| Period 1 title | Overall period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Subject |

Arms

| | |
|------------------------------|------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Fibrin Sealant Grifols |

Arm description:

Subjects topically applied FS Grifols, which consisted of component 1: human fibrinogen (80 mg/mL) and component 2: human thrombin with calcium chloride (500 IU/mL) solutions filled in syringes and assembled on a syringe holder.

| | |
|--|-----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | FS Grifols |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Transdermal spray, solution |
| Routes of administration | Topical |

Dosage and administration details:

The FE Grifols solution was applied topically via drip or spray application.

| | |
|------------------|--------|
| Arm title | EVICEL |
|------------------|--------|

Arm description:

Subjects topically applied EVICEL, which consisted of component 1: Concentrate of human fibrinogen (BAC 2) (55-85 mg/mL) and component 2: human thrombin (800-1200 IU/mL) solutions. The 2 components (BAC2 and thrombin) were mixed and applied topically.

| | |
|--|-----------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | EVICEL |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Transdermal spray, solution |
| Routes of administration | Topical |

Dosage and administration details:

The EVICEL solution was applied topically via drip or spray application.

| Number of subjects in period 1 | Fibrin Sealant Grifols | EVICEL |
|---------------------------------------|-------------------------------|---------------|
| Started | 95 | 91 |
| Parenchymous Surgery | 46 | 43 |
| Soft Tissue Surgery | 45 | 44 |
| Safety Population | 91 | 87 |
| Completed | 87 | 84 |
| Not completed | 8 | 7 |
| Consent withdrawn by subject | - | 1 |
| Death | 1 | 2 |
| Screen failure | 3 | 1 |
| Lost to follow-up | 3 | - |
| Reason not specified | 1 | 3 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | Fibrin Sealant Grifols |
|-----------------------|------------------------|

Reporting group description:

Subjects topically applied FS Grifols, which consisted of component 1: human fibrinogen (80 mg/mL) and component 2: human thrombin with calcium chloride (500 IU/mL) solutions filled in syringes and assembled on a syringe holder.

| | |
|-----------------------|--------|
| Reporting group title | EVICEL |
|-----------------------|--------|

Reporting group description:

Subjects topically applied EVICEL, which consisted of component 1: Concentrate of human fibrinogen (BAC 2) (55-85 mg/mL) and component 2: human thrombin (800-1200 IU/mL) solutions. The 2 components (BAC2 and thrombin) were mixed and applied topically.

| Reporting group values | Fibrin Sealant Grifols | EVICEL | Total |
|---|------------------------|-----------------|-------|
| Number of subjects | 95 | 91 | 186 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 8.43 ± 6.108 | 8.84 ± 6.320 | - |
| Gender categorical Units: Subjects | | | |
| Female | 40 | 30 | 70 |
| Male | 55 | 61 | 116 |

End points

End points reporting groups

| | |
|---|------------------------|
| Reporting group title | Fibrin Sealant Grifols |
| Reporting group description: Subjects topically applied FS Grifols, which consisted of component 1: human fibrinogen (80 mg/mL) and component 2: human thrombin with calcium chloride (500 IU/mL) solutions filled in syringes and assembled on a syringe holder. | |
| Reporting group title | EVICEL |
| Reporting group description: Subjects topically applied EVICEL, which consisted of component 1: Concentrate of human fibrinogen (BAC 2) (55-85 mg/mL) and component 2: human thrombin (800-1200 IU/mL) solutions. The 2 components (BAC2 and thrombin) were mixed and applied topically. | |

Primary: Percentage of Subjects Achieving Hemostasis Within 4 Minutes After Treatment Start (T4)

| | |
|---|---|
| End point title | Percentage of Subjects Achieving Hemostasis Within 4 Minutes After Treatment Start (T4) |
| End point description: Hemostasis is defined as Grade 0 bleeding per 5-point validated bleeding severity scale (0=no bleeding and 4=Unidentified or inaccessible spurting or gush) at the target bleeding site (TBS) according to the investigator's (surgeon's) judgment, so that the surgical closure of the exposed field could begin. Modified ITT (mITT) population included all subjects in the ITT population who meet the intra-operative enrollment criteria, and thus treated with any amount of investigational product (IP). Overall number analysed are the number of participants with haemostasis by 4 minutes. 'n' indicates the number of participants with parenchymous and soft tissue surgery with data available for analysis. Percentage are rounded off the single decimal point. | |
| End point type | Primary |
| End point timeframe: From start of treatment until 4 minutes after treatment start (Day 1) | |

| End point values | Fibrin Sealant Grifols | EVICEL | | |
|---------------------------------|------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 87 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Parenchymous Surgery (n=46, 43) | 100.0 | 100.0 | | |
| Soft Tissue Surgery (n=45,44) | 93.3 | 90.9 | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Hemostasis by 4 Minutes (Parenchymous) |
| Comparison groups | Fibrin Sealant Grifols v EVICEL |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 178 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative risk |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 1.09 |

| | |
|---|---------------------------------------|
| Statistical analysis title | Hemostasis by 4 Minutes (Soft Tissue) |
| Comparison groups | Fibrin Sealant Grifols v EVICEL |
| Number of subjects included in analysis | 178 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative risk |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.91 |
| upper limit | 1.16 |

Secondary: Cumulative Percentage of Subjects Achieving Hemostasis at the TBS by the 7 Minutes After Treatment Start (T7)

| | |
|-----------------|---|
| End point title | Cumulative Percentage of Subjects Achieving Hemostasis at the TBS by the 7 Minutes After Treatment Start (T7) |
|-----------------|---|

End point description:

Hemostasis = Grade 0 bleeding per 5-point validated bleeding severity scale (0=no bleeding and 4=Unidentified or inaccessible spurting or gush) at the TBS according to the investigator's (surgeon's) judgment, so that surgical closure of the exposed field could begin. Cumulative percentage of subjects achieving hemostasis at the TBS by time points of T7 defined as an absence/cessation of bleeding (Grade 0) at the TBS by that time point without occurrence of rebleeding, Grade 3 or Grade 4 bleeding, use of alternative hemostatic treatment, and reapplication of study treatment after T4 and until TClosure. mITT population=all subjects in ITT population who meet intra-operative enrollment criteria, and thus treated with any amount of investigational product (IP). Overall number analysed are number of participants with haemostasis by 7 minutes. 'n' = number of participants with parenchymous and soft tissue surgery with data for analysis. Percentages are rounded off a single decimal point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From start of treatment to 7 minutes after start of treatment (Day 1)

| End point values | Fibrin Sealant Grifols | EVICEL | | |
|--------------------------------|------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 87 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Parenchymous Surgery (n=46,43) | 100.0 | 100.0 | | |
| Soft Tissue Surgery (n=45,44) | 100.0 | 100.0 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Hemostasis by 7 Minutes (Parenchymous) |
| Comparison groups | Fibrin Sealant Grifols v EVICEL |
| Number of subjects included in analysis | 178 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative risk |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 1.09 |

| | |
|---|---------------------------------------|
| Statistical analysis title | Hemostasis by 7 Minutes (Soft tissue) |
| Comparison groups | Fibrin Sealant Grifols v EVICEL |
| Number of subjects included in analysis | 178 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative risk |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 1.09 |

Secondary: Cumulative Percentage of Subjects Achieving Hemostasis at the Target Bleeding Site by 10 Minutes After Treatment Start (T10)

| | |
|-----------------|--|
| End point title | Cumulative Percentage of Subjects Achieving Hemostasis at the Target Bleeding Site by 10 Minutes After Treatment Start (T10) |
|-----------------|--|

End point description:

Hemostasis is defined as Grade 0 bleeding at the TBS according to the investigator's (surgeon's) judgment, so that the surgical closure of the exposed field could begin. The cumulative percentage of subjects achieving hemostasis at the TBS by the time points of T10 defined as an absence/cessation of bleeding (Grade 0) at the TBS by that time point without occurrence of rebleeding, Grade 3 or Grade 4 bleeding, use of alternative hemostatic treatment, and reapplication of study treatment after T4 and until TClosure. mITT population included all participants in the ITT population who meet the intra-operative enrollment criteria and thus treated with any amount of IP. Overall number analyzed are the number of participants with haemostasis by 10 minutes. 'n' indicates number analyzed are the number of participants with parenchymous and soft tissue surgery with data available for analysis. Percentages are rounded off the single decimal point.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From start of treatment to 10 minutes after start of treatment (Day 1)

| End point values | Fibrin Sealant Grifols | EVICEL | | |
|--------------------------------|------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 90 | 87 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Parenchymous Surgery (n=45,43) | 97.8 | 100.0 | | |
| Soft Tissue Surgery (n=45,44) | 100.0 | 100.0 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Hemostasis by 10 Minutes (Parenchymous) |
| Comparison groups | Fibrin Sealant Grifols v EVICEL |
| Number of subjects included in analysis | 177 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative risk |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.94 |
| upper limit | 1.02 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Hemostasis by 10 Minutes (Soft tissue) |
| Comparison groups | Fibrin Sealant Grifols v EVICEL |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 177 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | < 0.001 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Relative risk |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 1.09 |

Secondary: Percentage of Participants With Treatment Failures

| | |
|---|--|
| End point title | Percentage of Participants With Treatment Failures |
| End point description: | |
| <p>Subjects were considered treatment failures if there is persistent bleeding at TBS beyond T4. Grade 3/Grade 4 breakthrough bleeding from TBS that jeopardizes subject safety according to investigator's judgment at any moment during 10-minute observational period and until TClosure. Use of alternative hemostatic treatments or maneuvers (other than study treatment) at TBS during 10-minute observational period and until TClosure, or use of study treatment at TBS beyond T4 and until TClosure. Rebleeding (Grade ≥ 1) at TBS after assessment of primary efficacy endpoint at T4 and until TClosure. mITT population: all participants in ITT population who meet intra-operative enrollment criteria and thus treated with any amount of IP. Overall number analyzed are number of participants with haemostasis by 4 minutes. 'n' indicates number of participants with parenchymous and soft tissue surgery with data available for analysis. Percentages are rounded off a single decimal point.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| From start of treatment up to 10 minutes after start of treatment and until the time of completion of surgical closure (Day 1) | |

| End point values | Fibrin Sealant Grifols | EVICEL | | |
|--------------------------------|---------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 91 | 87 | | |
| Units: Subjects | | | | |
| Parenchymous Surgery (n=46,43) | 0 | 0 | | |
| Soft Tissue Surgery (n=45,44) | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing informed consent form through the final study visit (30 ± 7 days post operative)

Adverse event reporting additional description:

The Safety population included all subjects who receive any amount of IP

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 25.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | EVICEL |
|-----------------------|--------|

Reporting group description:

Subjects received EVICEL, which consists of component 1: Concentrate of human fibrinogen (BAC 2) (55-85 mg/mL) and component 2: human thrombin human thrombin (800-1200 IU/mL) solutions. The 2 components (BAC2 and thrombin) were mixed and applied topically.

| | |
|-----------------------|------------------------|
| Reporting group title | Fibrin Sealant Grifols |
|-----------------------|------------------------|

Reporting group description:

Subjects received FS Grifols, which consists of component 1: human fibrinogen (80 mg/mL) and component 2: human thrombin with calcium chloride (500 IU/mL) solutions filled in syringes and assembled on a syringe holder.

| Serious adverse events | EVICEL | Fibrin Sealant Grifols | |
|---|-----------------|------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 87 (10.34%) | 8 / 91 (8.79%) | |
| number of deaths (all causes) | 2 | 1 | |
| number of deaths resulting from adverse events | 2 | 1 | |
| Investigations | | | |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 91 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 91 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 87 (1.15%) | 1 / 91 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Blood and lymphatic system disorders | | | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 91 (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 | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 91 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 2 / 91 (2.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 91 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 91 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 91 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus paralytic | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 91 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intussusception | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 91 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 91 (1.10%) | |
| 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 | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 91 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 91 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 91 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 91 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 91 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 91 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 91 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 91 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 91 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | EVICEL | Fibrin Sealant Grifols | |
|---|------------------|------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 87 (14.94%) | 20 / 91 (21.98%) | |
| Investigations | | | |
| Blood magnesium decreased | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 91 (1.10%) | |
| occurrences (all) | 0 | 1 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 1 / 91 (1.10%) | |
| occurrences (all) | 1 | 1 | |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 91 (1.10%) | |
| occurrences (all) | 0 | 1 | |
| Platelet count increased | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 91 (1.10%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|--|----------------|----------------|--|
| Injury, poisoning and procedural complications | | | |
| Anaemia postoperative | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 91 (1.10%) | |
| occurrences (all) | 0 | 1 | |
| Mechanical ventilation complication | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 91 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 91 (1.10%) | |
| occurrences (all) | 0 | 1 | |
| Procedural vomiting | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 91 (1.10%) | |
| occurrences (all) | 0 | 1 | |
| Wound complication | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 1 / 91 (1.10%) | |
| occurrences (all) | 0 | 1 | |
| Wound dehiscence | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 2 / 91 (2.20%) | |
| occurrences (all) | 0 | 2 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 87 (0.00%) | 2 / 91 (2.20%) | |
| occurrences (all) | 0 | 2 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 87 (3.45%) | 2 / 91 (2.20%) | |
| occurrences (all) | 3 | 2 | |
| General disorders and administration site conditions | | | |
| Generalised oedema | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 91 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 87 (5.75%) | 0 / 91 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Gastrointestinal disorders | | | |

| | | | |
|--|---------------------|---------------------|--|
| Abdominal distension subjects affected / exposed occurrences (all) | 0 / 87 (0.00%) 0 | 2 / 91 (2.20%) 2 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 1 / 87 (1.15%) 1 | 0 / 91 (0.00%) 0 | |
| Constipation subjects affected / exposed occurrences (all) | 1 / 87 (1.15%) 1 | 0 / 91 (0.00%) 0 | |
| Intra-abdominal fluid collection subjects affected / exposed occurrences (all) | 0 / 87 (0.00%) 0 | 1 / 91 (1.10%) 1 | |
| Melaena subjects affected / exposed occurrences (all) | 0 / 87 (0.00%) 0 | 1 / 91 (1.10%) 1 | |
| Nausea subjects affected / exposed occurrences (all) | 2 / 87 (2.30%) 2 | 1 / 91 (1.10%) 1 | |
| Vomiting subjects affected / exposed occurrences (all) | 3 / 87 (3.45%) 3 | 5 / 91 (5.49%) 5 | |
| Reproductive system and breast disorders Acquired hydrocele subjects affected / exposed occurrences (all) | 1 / 87 (1.15%) 0 | 0 / 91 (0.00%) 0 | |
| Respiratory, thoracic and mediastinal disorders Atelectasis subjects affected / exposed occurrences (all) | 0 / 87 (0.00%) 0 | 1 / 91 (1.10%) 1 | |
| Bronchospasm subjects affected / exposed occurrences (all) | 1 / 87 (1.15%) 1 | 1 / 91 (1.10%) 1 | |
| Cough subjects affected / exposed occurrences (all) | 1 / 87 (1.15%) 1 | 0 / 91 (0.00%) 0 | |
| Epistaxis | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 87 (0.00%) 0 | 1 / 91 (1.10%) 1 | |
| Pleural effusion subjects affected / exposed occurrences (all) | 0 / 87 (0.00%) 0 | 1 / 91 (1.10%) 1 | |
| Pneumothorax subjects affected / exposed occurrences (all) | 0 / 87 (0.00%) 0 | 1 / 91 (1.10%) 1 | |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 0 / 87 (0.00%) 0 | 1 / 91 (1.10%) 1 | |
| Infections and infestations Bacteraemia subjects affected / exposed occurrences (all) | 0 / 87 (0.00%) 0 | 1 / 91 (1.10%) 1 | |
| Pneumonia subjects affected / exposed occurrences (all) | 1 / 87 (1.15%) 1 | 0 / 91 (0.00%) 0 | |
| Postoperative abscess subjects affected / exposed occurrences (all) | 1 / 87 (1.15%) 1 | 0 / 91 (0.00%) 0 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 87 (0.00%) 0 | 1 / 91 (1.10%) 1 | |
| Wound infection subjects affected / exposed occurrences (all) | 0 / 87 (0.00%) 0 | 1 / 91 (1.10%) 1 | |
| Metabolism and nutrition disorders Acidosis subjects affected / exposed occurrences (all) | 1 / 87 (1.15%) 1 | 0 / 91 (0.00%) 0 | |
| Decreased appetite subjects affected / exposed occurrences (all) | 0 / 87 (0.00%) 0 | 1 / 91 (1.10%) 1 | |
| Hypoalbuminaemia | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 91 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 87 (1.15%) | 0 / 91 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 21 May 2019 | The purpose of the amendment was to revise to describe the modifications made to the FS Grifols container and packaging and revise to describe the modified procedure for the spray application because the original applicator was replaced. The new applicator is a Dual Applicator tip, which does not require gas pressure and can be used for both drip and spray applications of the IP. |
| 06 November 2019 | The purpose of the amendment was to update the number of subjects allowed to enroll into the study. To update to clarify that subjects participating or planning to participate in any other study will not be allowed to enroll in this study. To revise to clarify the amount of IP allowed for each age group and to correct the recommended psi for EVICEL application. |
| 02 November 2021 | The purpose of the amendment was to update to allow enrollment of preterm (up to gestational age <37 week) and term newborn infants (0 to 27 days) undergoing emergency (non-elective) surgery, per FDA advice. To revise to allow for flexibility in enrollment if hepatic surgeries are less than 50%. To update number of subjects planned in case of under or over enrollment. To update to further define and clarify the demographic information to be recorded and to clarify all Screening and to updated to describe FDA regulations and guidance for recording race information. |
| 11 November 2021 | The purpose of the amendment was a administrative change to remove incorrect headers. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported