



Clinical trial results:

A Prospective, Randomized, Controlled Study Evaluating EVICEL® Fibrin Sealant as an Adjunct to Haemostasis During Abdominal, Retroperitoneal, Pelvic or Thoracic (Non-Cardiac) Surgery in Paediatric Patients

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2013-003401-26 |
| Trial protocol | GB BE |
| Global end of trial date | 17 May 2019 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 03 December 2019 |
| First version publication date | 03 December 2019 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | 400-12-006 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02227706 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | ETHICON Inc |
| Sponsor organisation address | Route 22 West, Somerville, United States, 08876-0262 |
| Public contact | Leonie Rynn, ETHICON Inc, 001 9082182492, lrynn1@its.jnj.com |
| Scientific contact | Leonie Rynn, ETHICON Inc, 001 9082182492, lrynn1@its.jnj.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001149-PIP01-11 |
| 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 | 22 July 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 May 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 May 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and effectiveness of EVICEL® as an adjunct to achieve haemostasis during surgery in paediatric patients.

Protection of trial subjects:

Study information was presented to the patient and their legal guardian by a trained member of the research team. The final taking of informed consent was completed by the Investigator or sub-investigator when the potential participant and their legal guardian were completely satisfied with the information presented.

Venepuncture was required, however we minimised the number required and where possible results that were already available were used rather than repeating the test. All visits were conducted at times where the patient would routinely attend the hospital with the option to conduct the 30 day follow-up visit by telephone.

Physical examinations were undertaken by a trained member of the research team in a private area or room, or if this procedure was completed routinely upon admission to the hospital it was not repeated.

The study was reviewed and approved by the respective ethics committees in the countries where the study was being conducted.

Background therapy:

None.

Evidence for comparator:

With a clinical history spanning more than 50 years, SURGICEL® has been used as an adjunct to achieve and accelerate haemostasis when various types of bleeding were observed intra-operatively. The product can be placed on the source of bleeding with manual compression to facilitate haemostasis and was therefore considered a suitable control product for use in this study.

| | |
|---|------------------|
| Actual start date of recruitment | 05 November 2014 |
| 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 | Canada: 4 |
| Country: Number of subjects enrolled | United Kingdom: 36 |
| Worldwide total number of subjects | 40 |
| EEA total number of subjects | 36 |

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) | 7 |
| Children (2-11 years) | 13 |
| Adolescents (12-17 years) | 20 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The first subject was recruited on 5th November 2014 and the last subject was recruited on 17th April 2019. The last subject's last visit took place on 17th May 2019.

Pre-assignment

Screening details:

Prospective subjects were screened within 21 days prior to surgery. Prior to any study related procedures, subjects and/or parent or legal representative were fully informed of all aspects of the study. Subjects and/or their parent or legal representative were asked to sign a Consent Form or assent, as applicable.

Period 1

| | |
|------------------------------|------------------------------------|
| Period 1 title | Full Analysis Set (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

N/A

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | EVICEL® |

Arm description:

EVICEL® is a human plasma derived fibrin sealant consisting of two components: (1) Biologically Active Component 2 (BAC2), a concentrate of human clottable protein (containing mainly human fibrinogen and fibrinectin), and (2) human thrombin.

| | |
|--|----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | EVICEL® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for sealant |
| Routes of administration | Epilesional use |

Dosage and administration details:

For each subject, at least one EVICEL® (BAC2 and Thrombin) kit was thawed and available for administration prior to randomization. EVICEL® was to be sprayed or dripped onto the tissue to produce a thin, even layer.

| | |
|------------------|-----------|
| Arm title | SURGICEL® |
|------------------|-----------|

Arm description:

SURGICEL® Absorbable hemostat is a sterile absorbable knitted fabric prepared by controlled oxidation of regenerated cellulose.

| | |
|--|--------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | SURGICEL® Original |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Sealant matrix |
| Routes of administration | Topical use |

Dosage and administration details:

For subjects randomized to SURGICEL®, the product was to be applied and held firmly on the TBS, immediately after randomization according to the product instructions for use.

| Number of subjects in period 1 | EVICEL® | SURGICEL® |
|---------------------------------------|---------|-----------|
| Started | 20 | 20 |
| Completed | 20 | 20 |

Baseline characteristics

Reporting groups

| | |
|---|-----------|
| Reporting group title | EVICEL® |
| Reporting group description: EVICEL® is a human plasma derived fibrin sealant consisting of two components: (1) Biologically Active Component 2 (BAC2), a concentrate of human clottable protein (containing mainly human fibrinogen and fibrinectin), and (2) human thrombin. | |
| Reporting group title | SURGICEL® |
| Reporting group description: SURGICEL® Absorbable hemostat is a sterile absorbable knitted fabric prepared by controlled oxidation of regenerated cellulose. | |

| Reporting group values | EVICEL® | SURGICEL® | Total |
|--|-------------|-------------|-------|
| Number of subjects | 20 | 20 | 40 |
| Age Categorical Units: Subjects | | | |
| Infants and toddlers (28 days-23 months) | 5 | 2 | 7 |
| Children (2-11 years) | 4 | 9 | 13 |
| Adolescents (12-17 years) | 11 | 9 | 20 |
| Age Continuous Units: years | | | |
| arithmetic mean | 9.4 | 9.0 | |
| full range (min-max) | 0.9 to 17.0 | 1.0 to 17.0 | - |
| Gender Categorical Units: Subjects | | | |
| Female | 11 | 7 | 18 |
| Male | 9 | 13 | 22 |

Subject analysis sets

| | |
|---|-------------------|
| Subject analysis set title | Full Analysis Set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All randomised subjects | |
| Subject analysis set title | Per Protocol |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Full analysis set who had no major protocol deviations | |
| Subject analysis set title | Safety Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All subjects who received treatment | |

| Reporting group values | Full Analysis Set | Per Protocol | Safety Set |
|------------------------------------|-------------------|--------------|------------|
| Number of subjects | 40 | 38 | 40 |
| Age Categorical Units: Subjects | | | |

| | | | |
|--|-------------|-------------|-------------|
| Infants and toddlers (28 days-23 months) | 7 | 7 | 7 |
| Children (2-11 years) | 13 | 13 | 13 |
| Adolescents (12-17 years) | 20 | 18 | 20 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 9.2 | 8.9 | 9.2 |
| full range (min-max) | 0.9 to 17.0 | 0.9 to 17.0 | 0.9 to 17.0 |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 18 | 18 | 18 |
| Male | 22 | 20 | 22 |

End points

End points reporting groups

| | |
|---|-------------------|
| Reporting group title | EVICEL® |
| Reporting group description: EVICEL® is a human plasma derived fibrin sealant consisting of two components: (1) Biologically Active Component 2 (BAC2), a concentrate of human clottable protein (containing mainly human fibrinogen and fibrinectin), and (2) human thrombin. | |
| Reporting group title | SURGICEL® |
| Reporting group description: SURGICEL® Absorbable hemostat is a sterile absorbable knitted fabric prepared by controlled oxidation of regenerated cellulose. | |
| Subject analysis set title | Full Analysis Set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All randomised subjects | |
| Subject analysis set title | Per Protocol |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Full analysis set who had no major protocol deviations | |
| Subject analysis set title | Safety Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All subjects who received treatment | |

Primary: Absolute Time to Haemostasis

| | |
|--|---|
| End point title | Absolute Time to Haemostasis ^[1] |
| End point description: Absolute time to haemostasis, defined as absolute time when there was no detectable bleeding at the Target Bleeding Site (TBS) | |
| End point type | Primary |
| End point timeframe: From randomisation | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The primary effectiveness endpoint is summarized descriptively by treatment group.

| End point values | EVICEL® | SURGICEL® | | |
|----------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: Minutes | | | | |
| median (confidence interval 95%) | | | | |
| Absolute time to haemostasis | 4.0 (3.3 to 4.7) | 4.0 (2.9 to 8.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostasis at Target Bleeding Site at 4 Minutes

| | |
|-----------------|--|
| End point title | Haemostasis at Target Bleeding Site at 4 Minutes |
|-----------------|--|

End point description:

Haemostasis at 4 Minutes

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

End point timeframe:

Intra-operatively from randomisation to 4 minutes after randomisation

| End point values | EVICEL® | SURGICEL® | Full Analysis Set | |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 20 | 20 | 40 | |
| Units: Subject | | | | |
| Haemostasis at 4 Minutes | 16 | 13 | 29 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostasis at Target Bleeding Site at 7 Minutes

| | |
|-----------------|--|
| End point title | Haemostasis at Target Bleeding Site at 7 Minutes |
|-----------------|--|

End point description:

Haemostasis at 7 Minutes

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

End point timeframe:

Intra-operatively from randomisation to 7 minutes after randomisation

| End point values | EVICEL® | SURGICEL® | Full Analysis Set | |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 20 | 20 | 40 | |
| Units: Subject | | | | |
| Haemostasis at 7 Minutes | 20 | 16 | 36 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Haemostasis at Target Bleeding Site at 10 Minutes

| | |
|-----------------|---|
| End point title | Haemostasis at Target Bleeding Site at 10 Minutes |
|-----------------|---|

| | |
|--|-----------|
| End point description: Haemostasis at 10 Minutes | |
| End point type | Secondary |
| End point timeframe: Intra-operatively from randomisation to 10 minutes after randomisation | |

| End point values | EVICEL® | SURGICEL® | Full Analysis Set | |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 20 | 20 | 40 | |
| Units: Subject | | | | |
| Haemostasis at 10 Minutes | 19 | 18 | 37 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Treatment Failures

| | |
|--|---------------------------------|
| End point title | Incidence of Treatment Failures |
| End point description: Defined as haemostasis not achieved within 10 minutes or bleeding requiring treatment other than re-application of the assigned haemostatic adjunct within 10 minutes. | |
| End point type | Secondary |
| End point timeframe: 10 minutes | |

| End point values | EVICEL® | SURGICEL® | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: Number of subjects (failure) | 1 | 5 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects with a Thrombotic Event

| | |
|------------------------|--|
| End point title | Number of Subjects with a Thrombotic Event |
| End point description: | |
| End point type | Other pre-specified |

End point timeframe:

From randomisation up to 30 days (+/- 14 days) following surgery

| End point values | EVICEL® | SURGICEL® | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: Subjects | | | | |
| Number of subjects with thrombotic events | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects with an Adverse Event Related to Re-bleeding at Target Bleeding Site

| | |
|-----------------|---|
| End point title | Number of Subjects with an Adverse Event Related to Re-bleeding at Target Bleeding Site |
|-----------------|---|

End point description:

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

From randomisation to 30 days (+/- 14 days) following surgery

| End point values | EVICEL® | SURGICEL® | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 20 | | |
| Units: Subject | | | | |
| Subjects with AE related to re-bleeding at TBS | 1 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were collected from point of randomisation, during the procedure, throughout hospital admission and until completion of the 30 day (+/-14 day) follow up visit.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

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

Reporting group description:

EVICEL® is a human plasma derived fibrin sealant consisting of two components: (1) Biologically Active Component 2 (BAC2), a concentrate of human clottable protein (containing mainly human fibrinogen and fibrinectin), and (2) human thrombin.

| | |
|-----------------------|-----------|
| Reporting group title | SURGICEL® |
|-----------------------|-----------|

Reporting group description:

SURGICEL® Absorbable hemostat is a sterile absorbable knitted fabric prepared by controlled oxidation of regenerated cellulose.

| Serious adverse events | EVICEL® | SURGICEL® | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 20 (20.00%) | 3 / 20 (15.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Castleman's disease | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) | |
| 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 | | | |
| Procedural complication | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Ureteral stent removal | | | |

| | | | |
|---|--|----------------|--|
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (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 | Additional description: Hypoxic Brain Injury | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Urinary incontinence | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (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 | | | |
| Varicella | Additional description: Chicken Pox | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (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 | EVICEL® | SURGICEL® | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 18 / 20 (90.00%) | 20 / 20 (100.00%) | |
| Vascular disorders | | | |

| | | | |
|---|----------------------|----------------------|--|
| Haemorrhage subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 2 / 20 (10.00%) 2 | |
| Hypertension subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 2 / 20 (10.00%) 2 | |
| Hypotension subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | 2 / 20 (10.00%) 3 | |
| Surgical and medical procedures Wound drainage subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Device occlusion subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Pain subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | 0 / 20 (0.00%) 0 | |
| Pyrexia subjects affected / exposed occurrences (all) | 8 / 20 (40.00%) 9 | 6 / 20 (30.00%) 7 | |
| Swelling subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Reproductive system and breast disorders Testicular pain subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| Atelectasis | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 2 / 20 (10.00%) | |
| occurrences (all) | 0 | 2 | |
| Cough | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 3 / 20 (15.00%) | |
| occurrences (all) | 1 | 3 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 0 | 1 | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 0 | 1 | |
| Hyperventilation | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Neonatal aspiration | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 0 | 1 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 0 | 1 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory depression | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tachypnoea | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 0 | 1 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 1 | 1 | |
| Investigations | | | |

| | | | |
|--|----------------------|----------------------|--|
| Blood potassium decreased subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| C-reactive protein increased subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 2 / 20 (10.00%) 2 | |
| Oxygen saturation decreased subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 2 / 20 (10.00%) 3 | |
| Respiratory rate decreased subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 20 (0.00%) 0 | |
| Respiratory rate increased subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 20 (0.00%) 0 | |
| Urine output decreased subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | 0 / 20 (0.00%) 0 | |
| White blood cell count increased subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Injury, poisoning and procedural complications | | | |
| Contusion subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Procedural complication subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Procedural pain subjects affected / exposed occurrences (all) | 7 / 20 (35.00%) 8 | 5 / 20 (25.00%) 5 | |
| Wound complication | | | |

| | | | |
|---|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 1 / 20 (5.00%) 1 | |
| Wound secretion subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Cardiac disorders | | | |
| Bradycardia subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 2 / 20 (10.00%) 2 | |
| Tachycardia subjects affected / exposed occurrences (all) | 3 / 20 (15.00%) 3 | 6 / 20 (30.00%) 6 | |
| Nervous system disorders | | | |
| Convulsion subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Dizziness subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 20 (0.00%) 0 | |
| Headache subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 20 (0.00%) 0 | |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | 0 / 20 (0.00%) 0 | |
| Blood and lymphatic system disorders | | | |
| Coagulopathy subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | 0 / 20 (0.00%) 0 | |
| Febrile neutropenia subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 20 (0.00%) 0 | |
| Eye disorders | | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 20 (0.00%) 0 | |
| Gastrointestinal disorders | | | |

| | | |
|------------------------------|-----------------|-----------------|
| Abdominal discomfort | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 |
| Abdominal distension | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 |
| Abdominal pain | | |
| subjects affected / exposed | 5 / 20 (25.00%) | 3 / 20 (15.00%) |
| occurrences (all) | 5 | 3 |
| Abdominal pain lower | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 1 |
| Abdominal pain upper | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 2 / 20 (10.00%) |
| occurrences (all) | 0 | 2 |
| Constipation | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 2 / 20 (10.00%) |
| occurrences (all) | 1 | 2 |
| Diarrhoea | | |
| subjects affected / exposed | 3 / 20 (15.00%) | 4 / 20 (20.00%) |
| occurrences (all) | 3 | 4 |
| Gastrointestinal haemorrhage | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 1 |
| Ileus | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 1 |
| Mucous stools | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 |
| Nausea | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 2 / 20 (10.00%) |
| occurrences (all) | 2 | 2 |
| Teething | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 |

| | | | |
|--|----------------------|----------------------|--|
| Vomiting subjects affected / exposed occurrences (all) | 3 / 20 (15.00%) 3 | 6 / 20 (30.00%) 6 | |
| Skin and subcutaneous tissue disorders | | | |
| Blister subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | 1 / 20 (5.00%) 1 | |
| Decubitus ulcer subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 20 (0.00%) 0 | |
| Dermatitis diaper subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 20 (0.00%) 0 | |
| Livedo reticularis subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 20 (0.00%) 0 | |
| Pruritus subjects affected / exposed occurrences (all) | 2 / 20 (10.00%) 2 | 1 / 20 (5.00%) 1 | |
| Rash subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 2 / 20 (10.00%) 2 | |
| Rash erythematous subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Erythema subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 20 (0.00%) 0 | |
| Renal and urinary disorders | | | |
| Polyuria subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |

| | | | |
|---|---------------------|----------------------|--|
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 2 / 20 (10.00%) 2 | |
| Infections and infestations | | | |
| Candidiasis subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 20 (0.00%) 0 | |
| Infection subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 20 (0.00%) 0 | |
| Orchitis subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Pneumonia subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Post procedural infection subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 1 / 20 (5.00%) 1 | |
| Viral infection subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 20 (0.00%) 0 | |
| Wound infection subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 20 (0.00%) 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 20 (5.00%) 1 | |
| Fluid overload | | | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyponatraemic syndrome | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 0 | 1 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 3 / 20 (15.00%) | |
| occurrences (all) | 1 | 3 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Polydipsia | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 20 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 02 October 2013 | A number of up-dates were made including the following - Product application technique, product labeling and shipping; visit timelines; primary and secondary endpoint clarifications to align with the Paediatric Investigation Plan (PIP); up-dates to the description of the analysis for success/failure data; administrative up-dates |
| 31 July 2015 | A number of up-dates were made including the following - Addition of parenchymal organ bleeding; up-date to the definition of open procedure and infected field; airless spray accessory device added; administrative up-dates |
| 29 February 2016 | A number of up-dates were made including the following - Up-dated to reflect the change in age group specifications for study recruitment; up-dated to further define treatment failure; clarification on statistical analysis for primary and secondary endpoints, laboratory values and handling of missing data; administrative up-dates |
| 08 January 2018 | A number of up-dates were made including the following - Removal of age stratification; further clarification on open procedure definition; additional information on product storage conditions; product application clarifications; administrative up-dates |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Two subjects in the control arm were haemostatic at the TBS at 10 minutes however they subsequently rebled requiring additional treatment and were conservatively considered a failure for the secondary endpoint of Incidence of Treatment Failures.

Notes: