Clinical trial results:
A Prospective, Randomised, Controlled Study Evaluating EVARREST® Fibrin Sealant Patch in Controlling Mild or Moderate Hepatic Parenchyma or Soft Tissue Bleeding During Open Abdominal, Retroperitoneal, Pelvic and Thoracic (Non-Cardiac) Surgery in Paediatric Patients

Summary

EudraCT number	2013-003557-24
Trial protocol	GB BE
Global end of trial date	12 November 2021

Results information

Result version number	v1 (current)
This version publication date	27 May 2022
First version publication date	27 May 2022

Trial information

Trial identification

Sponsor protocol code	400-12-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02227992
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ETHICON Inc
Sponsor organisation address	1000 US Highway 202 South, Raritan, United States, NJ08869
Public contact	Patricia Schleckser, ETHICON Inc, pschleck@its.jnj.com
Scientific contact	Dr. Richard Kocharian, MD, PhD, ETHICON Inc, 1 908 642 3787, rkochar1@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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	29 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 October 2021
Global end of trial reached?	Yes
Global end of trial date	12 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and haemostatic effectiveness of EVARREST® Fibrin Sealant Patch (EVARREST®) when used as an adjunct to control mild or moderate soft tissue and parenchymal bleeding during open hepatic, abdominal, pelvic, retroperitoneal, and thoracic (non-cardiac) surgery in paediatric patients.

Protection of trial subjects:

Study information was presented to the patient (where applicable) and their legal guardian by a trained member of the research team. The final taking of the 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.

Venipuncture was required, however we minimised the number required and where possible results that were already available were used rather than repeating the test. Visits were conducted at times where the patient would routinely attend the hospital where possible.

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 Ethics Committee in the country where the study was being conducted.

Background therapy:

During surgery or in the surgical management of trauma, surgeons encounter bleeding from a variety of tissue types. The need to effectively manage haemostasis during surgery has had a strong influence on the development of modern surgical techniques. Bleeding during surgical procedures may manifest in many forms. It can be discrete or diffuse from a large surface area. It can be from large or small vessels; arterial (high pressure) or venous (low pressure) of high or low volume. It may be easily accessible, or it may originate from difficult to access sites. This bleeding may be of any intensity: mild, moderate, or severe. The selection of appropriate methods or products for the control of bleeding is dependent upon many factors, which include but are not limited to bleeding severity, anatomical location of the source and the proximity of adjacent critical structures, whether the bleeding is from a discrete source or from a broader surface area, visibility and precise identification of the source and access to the source. Tissue type and fragility/friability, coagulation system status and patient stability are also factors for consideration.

Haemostasis is a prerequisite for wound healing, and, under normal physiologic conditions, it is achieved by means of the coagulation cascade. Conventional methods to achieve haemostasis includes use of surgical techniques, sutures, ligatures or clips, and energy-based coagulation or cauterisation. When these conventional measures are ineffective or impractical, adjunctive haemostasis techniques and products are typically utilised, including topical absorbable haemostats.

Evidence for comparator:

With a clinical history spanning more than 60 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	31 July 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 40
Worldwide total number of subjects	40
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	11
Children (2-11 years)	22
Adolescents (12-17 years)	7
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 enrolled on 31st July 2014 and the last subject was recruited on 26th October 2021. The last subject's last visit took place on 12th November 2021.

Pre-assignment

Screening details:

Prospective subjects were screened within 21 days prior to surgery. Prior to any study related procedures, subjects were fully informed of all aspects of the study. Subjects or subject legal representative/parent were asked to sign a Consent Form. Assent process occurred when 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

Arms

Are arms mutually exclusive?	Yes
Arm title	EVARREST

Arm description: -

Arm type	Experimental
Investigational medicinal product name	EVARREST Fibrin Sealant Patch
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sealant matrix
Routes of administration	Topical use

Dosage and administration details:

Per protocol, subjects assigned to EVARREST received up to 6.9 square cm per kilogram of body weight. Where subject's body weight allowed, additional pads could be placed up to a maximum of four (4) units of the 4 x 4 inches (10.2 x 10.2 centimeters) or a maximum of eight (8) units of the 2 x 4 inches (5.1 x 10.2 centimeters) of EVARREST was allowed to be implanted covering the entire TBS and overlapped the TBS with a margin of 1-2 cm. After placement of the study product, firm manual continual manual compression was applied over the entire bleeding area until 4 minutes had lapsed from the time of randomisation. Maximum amount of EVARREST used in this study was 1 patch per subject.

Arm title	SURGICEL

Arm description: -

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:

The dosage and product administration were followed as per the product IFU. After placement of SURGICEL, firm manual continual manual compression was applied over the entire bleeding area until 4 minutes had lapsed from the time of randomisation. Maximum amount of SURGICEL used in this study was 2 kits per subject.

Number of subjects in period 1	EVARREST	SURGICEL
Started	20	20
Completed	19	19
Not completed	1	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	EVARREST
Reporting group description: -	
Reporting group title	SURGICEL
Reporting group description: -	

Reporting group values	EVARREST	SURGICEL	Total
Number of subjects	20	20	40
Age Categorical Units: Participants			
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)	6	5	11
Children (2-11 years)	11	11	22
Adolescents (12-17 years)	3	4	7
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
median	3.0	4.0	
full range (min-max)	0.8 to 13.0	0.3 to 14.0	-
Gender Categorical Units: Participants			
Female	9	7	16
Male	11	13	24
Race, Customized Units: Subjects			
White/Caucasian	18	17	35
Asian	0	1	1
Black/African American	1	0	1
Other	1	2	3
Ethnicity Units: Subjects			
Hispanic	1	2	3
Non-Hispanic	19	18	37

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:

All subjects in the Full Analysis Set with no major protocol deviations affecting the primary effectiveness endpoint (agreed prior to database lock)

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	33	40
Age Categorical Units: Participants			
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)	11	8	11
Children (2-11 years)	22	20	22
Adolescents (12-17 years)	7	5	7
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
median	3.0	3.0	3.0
full range (min-max)	0.3 to 14.0	0.3 to 14.00	0.3 to 14.0
Gender Categorical Units: Participants			
Female	16	12	16
Male	24	21	24
Race, Customized Units: Subjects			
White/Caucasian	35	28	35
Asian	1	1	1
Black/African American	1	1	1
Other	3	3	3
Ethnicity Units: Subjects			
Hispanic	3	2	3
Non-Hispanic	37	31	37

End points

End points reporting groups

Reporting group title	EVARREST
Reporting group description: -	
Reporting group title	SURGICEL
Reporting group description: -	
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:	
All subjects in the Full Analysis Set with no major protocol deviations affecting the primary effectiveness endpoint (agreed prior to database lock)	
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 haemostasis is defined as time lapsed from randomisation to the last moment in time at which detectable bleeding at the Target Bleeding Site was observed.	
End point type	Primary
End point timeframe:	
Intra-operatively from randomisation to last moment in time at which detectable bleeding at Target Bleeding Site was observed	
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: 95% confidence intervals for the median absolute time to haemostasis was conducted for the overall analysis only and is presented in the table for Absolute Time to Haemostasis	

End point values	EVARREST	SURGICEL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Minutes				
median (confidence interval 95%)	4.0 (4.00 to 4.00)	4.0 (4.00 to 7.62)		

Statistical analyses

No statistical analyses for this end point

Primary: Absolute Time to Haemostasis (Subjects in Paediatric Group (1 month (>= 28 days from birth) to <1 year)

End point title	Absolute Time to Haemostasis (Subjects in Paediatric Group (1

	month (>= 28 days from birth) to <1 year)[2]

End point description:

Absolute haemostasis is defined as time lapsed from randomisation to the last moment in time at which detectable bleeding at the Target Bleeding Site was observe

End point type	Primary

End point timeframe:

Randomisation to last moment in time at which detectable bleeding at Target Bleeding Site was observed

Notes:

[2] - 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: 95% confidence intervals were conducted for the overall analysis only and is presented in the table for Absolute Time to Haemostasis

End point values	EVARREST	SURGICEL	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1	3	4	
Units: Minutes				
median (full range (min-max))	4.0 (4.0 to 4.0)	6.0 (4.0 to 6.9)	5.0 (4.0 to 6.9)	

Statistical analyses

No statistical analyses for this end point

Primary: Absolute Time to Haemostasis (Subject in Paediatric group [>/= 1 year to < 18 years])

End point title	Absolute Time to Haemostasis (Subject in Paediatric group [>/= 1 year to < 18 years])[3]

End point description:

Absolute haemostasis is defined as time lapsed from randomisation to the last moment in time at which detectable bleeding at the Target Bleeding Site was observe

End point type	Primary

End point timeframe:

Randomisation to last moment in time at which detectable bleeding at Target Bleeding Site was observed

Notes:

[3] - 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: 95% confidence intervals were conducted for the overall analysis only and is presented in the table for Absolute Time to Haemostasis

End point values	EVARREST	SURGICEL	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	19	17	36	
Units: Minutes				
median (full range (min-max))	4.0 (4.0 to 117.0)	4.0 (4.0 to 39.0)	4.0 (4.0 to 117.0)	

Statistical analyses

No statistical analyses for this end point

Primary: Summary of Absolute Time to Haemostasis (Primary Effectiveness Endpoint) by Treatment and Age group

End point title	Summary of Absolute Time to Haemostasis (Primary Effectiveness Endpoint) by Treatment and Age group[4]

End point description:

Absolute haemostasis is defined as time lapsed from randomisation to the last moment in time at which detectable bleeding at the Target Bleeding Site was observed.

End point type	Primary

End point timeframe:

Randomisation to last moment in time at which detectable bleeding at Target Bleeding Site was observed

Notes:

[4] - 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: 95% confidence intervals were conducted for the overall analysis only and is presented in the table for Absolute Time to Haemostasis

End point values	EVARREST	SURGICEL	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	20[5]	20[6]	40[7]	
Units: Minutes				
median (full range (min-max))				
Infants and Toddlers (28 days to <24 months)	4.0 (4.0 to 4.0)	4.0 (4.0 to 6.9)	4.0 (4.0 to 6.9)	
Children (2 to 11 years)	4.0 (4.0 to 117.0)	4.0 (4.0 to 39.0)	4.0 (4.0 to 117.0)	
Adolescent (12 to <18 years)	4.0 (4.0 to 7.5)	4.0 (4.0 to 10.0)	4.0 (4.0 to 10.0)	
All subjects	4.0 (4.0 to 117.0)	4.0 (4.0 to 39.0)	4.0 (4.0 to 117.0)	

Notes:

[5] - Infants/Toddlers: 6 subjects
Children: 11 subjects
Adolescent: 3 subjects
All: 20 subjects
[6] - Infants/Toddlers: 5 subjects
Children: 11 subjects
Adolescent: 4 subjects
All: 20 subjects
[7] - Infants and Toddlers:
Children:
Adolescent:

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects Achieving Haemostatic Success at 4 minutes

End point title	Proportion of Subjects Achieving Haemostatic Success at 4 minutes

End point description:

Proportion of subjects achieving haemostatic success at 4 minutes following randomisation and no bleeding requiring treatment at the Target Bleeding Site occurs any time prior to final fascial closure

End point type	Secondary

End point timeframe:

Intra-operatively from randomisation to 4 minutes following randomisation

End point values	EVARREST	SURGICEL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Percentage				
number (confidence interval 95%)				
Proportion of subjects	80.0 (56.3 to 94.3)	60.0 (36.1 to 80.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects Ahieving Haemostatic Success at 10 minutes

End point title	Proportion of Subjects Ahieving Haemostatic Success at 10 minutes

End point description:

Proportion of subjects achieving haemostatic success at 4 minutes following randomisation and no bleeding requiring treatment at the Target Bleeding Site occurs any time prior to final fascial closure

End point type	Secondary

End point timeframe:

Intra-operatively from randomisation to 10 minutes following randomisation

End point values	EVARREST	SURGICEL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Percentage				
number (confidence interval 95%)				
Proportion of subjects	95.0 (75.1 to 99.9)	90.0 (68.3 to 98.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects With No Re-bleeding at Target Bleeding Site

End point title	Subjects With No Re-bleeding at Target Bleeding Site

End point description:

End point type	Secondary

End point timeframe:

Intra-operatively from randomisation up to the 30-day (+/- 14 days) follow-up visit

End point values	EVARREST	SURGICEL	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	20	20	40	
Units: Percentage				
number (not applicable)	95.0	85.0	90.0	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Additional Treatment at Target Bleeding Site

End point title	Additional Treatment at Target Bleeding Site

End point description:

Any treatment applied to the Target Bleeding Site following randomised treatment

End point type	Other pre-specified

End point timeframe:

Intra-operatively from application of randomised treatment to final fascial closure

End point values	EVARREST	SURGICEL	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	20	20	40	
Units: Participants	1	5	6	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects with at Least 1 Adverse Event Related to Re-bleeding at Target Bleeding Site

End point title	Number of Subjects with at Least 1 Adverse Event Related to Re-bleeding at Target Bleeding Site

End point description:

Sponsor Assessment - Events assessed as possibly related or related to re-bleeding at Target Bleeding Site

End point type	Other pre-specified

End point timeframe:

Product application to the 30 day (+/- 14 days) follow-up

End point values	EVARREST	SURGICEL	Safety Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	20	20[8]	40	
Units: Participants				
number (not applicable)	1	3	4	

Notes:

[8] - 1 SAE of bloody discharge was reported post-operatively & conservatively considered possibly related

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects with at Least 1 Thrombotic Adverse Event

End point title	Number of Subjects with at Least 1 Thrombotic Adverse Event
End point description:	
Sponsor assessment	
End point type	Other pre-specified
End point timeframe:	
Intra-operatively from randomisation to 30 day (+/- 14 days) follow-up visit	

End point values	EVARREST	SURGICEL	Safety Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	20	20	40	
Units: Participants				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Estimated Volume of Blood Loss

End point title	Estimated Volume of Blood Loss
End point description:	
Estimated volume of intra-operative blood loss (including but not limited to the Target Bleeding Site)	
End point type	Other pre-specified
End point timeframe:	
During surgery from first incision to final fascial closure	

End point values	EVARREST	SURGICEL	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	20	20	40	
Units: mL				
median (full range (min-max))	100.0 (0.0 to 800.0)	200.0 (15.0 to 2000.0)	150.0 (0.0 to 2000.0)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Blood and Blood Product Transfusion

End point title	Blood and Blood Product Transfusion

End point description:

End point type	Other pre-specified

End point timeframe:

Intra-operatively to 30-day (+/- 14 days) follow-up visit

End point values	EVARREST	SURGICEL	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	20	20	40	
Units: Participants				
number (not applicable)	12	11	23	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Blood and Blood Products Transfused

End point title	Blood and Blood Products Transfused

End point description:

End point type	Other pre-specified

End point timeframe:

Intra-operatively from first incision to the 30-day (+/- 14 days) follow-up visit

End point values	EVARREST	SURGICEL	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	20	20	40	
Units: Participants				
Packed Red Blood Cells:0 Unit	3	2	5	
Packed Red Blood Cells:1 Unit	4	4	8	
Packed Red Blood Cells:2 Units	4	3	7	
Packed Red Blood Cells:3 Units	1	1	2	
Packed Red Blood Cells:4 Units	0	0	0	
Packed Red Blood Cells:5 Units	0	0	0	
Packed Red Blood Cells:6 Units	0	1	1	
Whole Blood: 0 Unit	9	9	18	
Whole Blood: 1 Unit	2	1	3	
Whole Blood: 2 Units	1	1	2	
Fresh Frozen Plasma: 0 Unit	10	11	21	
Fresh Frozen Plasma: 1 Unit	0	0	0	
Fresh Frozen Plasma: 2 Units	1	0	1	
Fresh Frozen Plasma: 3 Units	0	0	0	
Fresh Frozen Plasma: 4 Units	0	0	0	
Fresh Frozen Plasma: 5 Units	1	0	1	
Platelets: 0 Unit	8	9	17	
Platelets: 1 Unit	3	1	4	
Platelets: 2 Units	1	0	1	
Platelets: 3 Units	0	1	1	
Cryoprecipitates: 0 Unit	12	11	23	
Other: 0 Unit	11	9	20	
Other: 1 Unit	0	1	1	
Other: 2 Units	1	1	2	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Laboratory Parameters - Haemoglobin, Haematocrit and Platelets

End point title	Laboratory Parameters - Haemoglobin, Haematocrit and Platelets

End point description:

End point type	Other pre-specified

End point timeframe:

Between baseline (up to 21 days prior to surgery) and post-operative hospital discharge

End point values	EVARREST	SURGICEL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: SI				
median (full range (min-max))				
Haemoglobin: g/L	0.0 (-56.0 to 43.0)	-10.0 (-150.0 to 44.0)		
Haematocrit: g/L	0.0 (-0.2 to 0.1)	-0.0 (-0.1 to 0.1)		
Platelet Count: (x10(9)/L)	-89.0 (-531.0 to 112.0)	-71.5 (-259.0 to 386.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Intra-operatively from randomisation up to and including the 30-day (+/- 14 days) follow-up visit

Adverse event reporting additional description:

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Only exacerbations of expected post operative pain based on the Investigator's judgment was reported as an Adverse Event.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	SURGICEL
Reporting group description: -	
Reporting group title	EVARREST

Reporting group description: -

Serious adverse events	SURGICEL	EVARREST	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 20 (25.00%)	4 / 20 (20.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Weight Decreased			
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	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neuroblastoma			
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	
Vascular disorders			
Bloody Discharge			
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			
Thrombocytopenia			
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	
Febrile neutropenia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intussusception			
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	
Localised intraabdominal fluid collection			
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	
Renal and urinary disorders			
Hematuria			
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	
Infections and infestations			
Device related 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	
Urinary tract infection			
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	

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

Non-serious adverse events	SURGICEL	EVARREST	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 20 (85.00%)	18 / 20 (90.00%)	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Hypotension			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	2 / 20 (10.00%)	3 / 20 (15.00%)	
occurrences (all)	2	3	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Puncture site discharge			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	9 / 20 (45.00%)	5 / 20 (25.00%)	
occurrences (all)	10	5	
Device occlusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			

Vulval oedema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Bradypnoea			
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	
Cough			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Pleural effusion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Pneumothorax			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Respiratory distress			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Wheezing			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Investigations			

Blood alkaline phosphate decreased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Haemoglobin decreased			
subjects affected / exposed	2 / 20 (10.00%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
International normalized ratio increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Neutrophil count increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Oxygen saturation decreased			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Urine output decreased			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
occurrences (all)	0	2	
Blood pressure increased			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Blood potassium decreased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Procedural hypotention			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Procedural pain			
subjects affected / exposed	7 / 20 (35.00%)	3 / 20 (15.00%)	
occurrences (all)	7	3	
Wound complication			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Wound secretion			

subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Anal injury			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Excoriation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Procedural haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	3 / 20 (15.00%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Tachycardia			
subjects affected / exposed	7 / 20 (35.00%)	10 / 20 (50.00%)	
occurrences (all)	9	10	
Nervous system disorders			
Horner’s syndrome			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Coagulopathy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Febrile neutropenia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 20 (10.00%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Abdominal pain upper			
subjects affected / exposed	2 / 20 (10.00%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	4 / 20 (20.00%)	2 / 20 (10.00%)	
occurrences (all)	4	2	
Dry mouth			
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	
Vomiting			
subjects affected / exposed	6 / 20 (30.00%)	6 / 20 (30.00%)	
occurrences (all)	7	7	
Constipation			
subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Haematemesis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	3 / 20 (15.00%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Swelling face			

subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	3 / 20 (15.00%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Decubitus ulcer			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Joint instability			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Candidiasis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Device related infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Clostridium difficile infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Escherichia infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			

subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 20 (10.00%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Hypoalbuminaemia			
subjects affected / exposed	2 / 20 (10.00%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Hypomagnesaemia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Hypophosphataemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Hypovolaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Metabolic acidosis			
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
04 December 2014	Protocol Amendment 1 was introduced to align the use of additional treatment at the TBS to previous adult studies. Additional clarification test was also added regarding eligible procedure types and information collected at the surgical visit. This amendment also introduced a new size of EVARREST patch (2 x 4 inch) and up-dated the number of mis-randomised subjects that would require summarisation in the FAS and Evaluable Analysis sets.
17 March 2016	Protocol Amendment 2 was introduced to change the sample size and age stratification as approved by the EMA under a PIP Modification. Reference to sample size was up-dated throughout, including statistical analysis section. Additional changes made at this included the definition of actively infected field which was added to exclusion criteria. A clarification to the assenting process was included. Pregnancy test at screening visit was removed and clarified that it should be with 24 hours of surgery for applicable patients and could be a serum or urine test. An up-date to the AE definition for post-operative pain was also added.
13 December 2016	Protocol Amendment 3 was introduced to update the TBS identification definition to align with adult studies. Height and weight were added to physical examination. The handling of EVARREST in the sterile field included additional information for clarity. Additional clarifications were made to when laboratory samples could be collected and the timepoint when concomitant medications were to be recorded from. Reference to subject initials was removed from the protocol as these were no longer being recorded. Up-dates to the description of EVARREST were included as well as previous clinical experience.
05 March 2018	Protocol Amendment 4 was introduced to remove fibrinogen from the coagulation sample as it was not required for the study. The period in which adverse events were to be entered into the EDC was also added in this amendment.

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.

This was a 40 subject enrolling only paediatric patients as part of a Paediatric Investigational Plan approved by the European Medicines Agency and UK Paediatric Investigation Plan approved by the MHRA.

Notes: