



Clinical trial results:

A Randomised Controlled Study to Evaluate the Efficacy and Safety of Fibrin Sealant, Vapour Heated, Solvent/Detergent Treated (FS VH S/D 500 s-apr) Compared to DuraSeal Dural Sealant as an Adjunct to Sutured Dural Repair in Cranial Surgery

Summary

EudraCT number	2015-005535-40
Trial protocol	DE CZ ES PL
Global end of trial date	22 August 2018

Results information

Result version number	v1 (current)
This version publication date	06 September 2019
First version publication date	06 September 2019

Trial information

Trial identification

Sponsor protocol code	3599-001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02891070
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Baxter Healthcare Corporation
Sponsor organisation address	1 Baxter Pkwy, Deerfield, United States, 60015
Public contact	Baxter Clinical Trials Disclosure Call Center, Baxter Healthcare Corporation, 224 948-7359, Global_CORP_ClinicalTrialsDisclosure@baxter.com
Scientific contact	Baxter Clinical Trials Disclosure Call Center, Baxter Healthcare Corporation, 224 948-7359, Global_CORP_ClinicalTrialsDisclosure@baxter.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 November 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	22 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of FS VH S/D 500 s-apr compared to DuraSeal Dural Sealant as an adjunct to sutured dural closure.

Protection of trial subjects:

In case of a continuous CSF leak in spite of treatment (i.e., treatment failure), rescue therapy using standard of care was permitted at the surgeon's choice (including use of other sealants, dural patches, etc. [excluding further use of the IP or control in either of the 2 groups]).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 October 2016
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: 36
Country: Number of subjects enrolled	Spain: 67
Country: Number of subjects enrolled	Czech Republic: 92
Country: Number of subjects enrolled	Germany: 29
Worldwide total number of subjects	224
EEA total number of subjects	188

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	178
From 65 to 84 years	46

85 years and over	0
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Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

It was expected to screen approximately 476 patients in order to randomize approximately 224 patients (with a minimal number of 56 PF procedures) and have 202 evaluable patients.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Tisseel

Arm description:

Investigational Product: FS VH S/D 500 s-apr (Tisseel) frozen 4 mL syringe

Arm type	Experimental
Investigational medicinal product name	Tisseel
Investigational medicinal product code	FS VH S/D 500 s-apr
Other name	
Pharmaceutical forms	Solution for sealant
Routes of administration	Epileisional use

Dosage and administration details:

Tisseel (FS VH S/D 500 s-apr), single use treatment, frozen 4 mL syringe, was administered intra-operatively with sutures during dural closure. Product was applied with cannula by dripping in a thin and continuous layer with a 5 mm overlap on each side of the sutured line, ensuring that all suture holes were covered.

Arm title	DuraSeal
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Arm description:

Control: DuraSeal 5 mL syringe

Arm type	Active comparator
Investigational medicinal product name	DuraSeal
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for sealant
Routes of administration	Epileisional use

Dosage and administration details:

DuraSeal Dural Sealant, single use treatment, was administered intra-operatively with sutures during dural closure. The product was applied with the DuraSeal System Applicator by spraying a thin (1 – 2 mm) coating, ensuring that all suture holes were covered.

Number of subjects in period 1	Tisseel	DuraSeal
Started	110	114
Completed	100	106
Not completed	10	8
Adverse event, serious fatal	3	-
Consent withdrawn by subject	1	2
Physician decision	-	1
Adverse event, non-fatal	1	-
Unknown	1	-
Lost to follow-up	4	4
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Tisseel
Reporting group description:	
Investigational Product: FS VH S/D 500 s-apr (Tisseel) frozen 4 mL syringe	
Reporting group title	DuraSeal
Reporting group description:	
Control: DuraSeal 5 mL syringe	

Reporting group values	Tisseel	DuraSeal	Total
Number of subjects	110	114	224
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	51.8	51.3	
standard deviation	± 14.24	± 14.85	-
Gender categorical Units: Subjects			
Female	66	65	131
Male	44	49	93
Race Units: Subjects			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	2	2	4
Native Hawaiian or Other Pacific Islander	0	0	0
White	97	101	198
Other	11	11	22

End points

End points reporting groups

Reporting group title	Tisseel
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Reporting group description:

Investigational Product: FS VH S/D 500 s-apr (Tisseel) frozen 4 mL syringe

Reporting group title	DuraSeal
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Reporting group description:

Control: DuraSeal 5 mL syringe

Subject analysis set title	Tisseel (PPS)
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Subject analysis set type	Per protocol
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Subject analysis set description:

Per Protocol Set (PPS) - The PPS was defined as a subset of the FAS. Patients with any major deviation that may have impacted the primary efficacy parameter were excluded from the PPS.

Subject analysis set title	DuraSeal (PPS)
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Subject analysis set type	Per protocol
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Subject analysis set description:

Per Protocol Set (PPS) - The PPS was defined as a subset of the FAS. Patients with any major deviation that may have impacted the primary efficacy parameter were excluded from the PPS.

Subject analysis set title	Tisseel (SAS)
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Safety Analysis Set (SAS) - Consisted of all patients who were treated with IP/Control. Patients were analyzed as treated.

Subject analysis set title	DuraSeal (SAS)
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Subject analysis set type	Safety analysis
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Subject analysis set description:

Safety Analysis Set (SAS) - Consisted of all patients who were treated with IP/Control. Patients were analyzed as treated.

Primary: Number of Participants with No CSF Leaks During and after Surgery

End point title	Number of Participants with No CSF Leaks During and after Surgery
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End point description:

Participants who have no intra-operative CSF leak from dural repair after up to two applications during Valsalva maneuver (25 cm H₂O for up to 5 - 10 seconds), or post-operative CSF leak within 30 (+3) days post-operatively. The Valsalva maneuver was performed by the anaesthesiologist to increase the intra-thoracic pressure (e.g., by increasing the positive end-expiratory pressure or by giving a large tidal volume and holding the inflating pressure) to approximately 25 cm H₂O, constantly for up to 5 - 10 seconds to transiently elevate the intracranial pressure and test for any CSF leaks. The suture line was to be watertight after up to two product/control applications and Valsalva maneuvers.

End point type	Primary
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End point timeframe:

Day 0 (Intra-operative) to Day 30 (+/-3 days) post-operative

End point values	Tisseel (PPS)	DuraSeal (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	95		
Units: Participants	76	87		

Statistical analyses

Statistical analysis title	Stats
Comparison groups	Tisseel (PPS) v DuraSeal (PPS)
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Method	Regression, Logistic
Parameter estimate	Mean difference (net)
Point estimate	-9.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.11
upper limit	2.54

Notes:

[1] - To demonstrate non-inferiority of Tisseel to DuraSeal for the primary endpoint, the lower limit of the 95% CI (based on normal approximation) for the difference in average predicted proportions had to be greater than -10%.

Secondary: Number of Participants with No Intra-Operative CSF Leaks following final Valsalva maneuver

End point title	Number of Participants with No Intra-Operative CSF Leaks following final Valsalva maneuver
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End point description:

Assessment of whether the suture line was not watertight causing CSF leaks after up to two product/control applications and Valsalva maneuvers.

End point type	Secondary
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End point timeframe:

Day 0 (Intra-operative)

End point values	Tisseel (PPS)	DuraSeal (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	95		
Units: Participants	89	95		

Statistical analyses

Secondary: Number of Participants with CSF Leaks within 30 (+3) days post-operatively

End point title	Number of Participants with CSF Leaks within 30 (+3) days post-operatively
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End point description:

Cerebrospinal fluid leak was defined as any overt flow, seepage, weeping, or sweating of CSF through the dura suture line, regardless of volume. All post-operative CSF leaks were primarily diagnosed based on a detailed history and physical examination, including neurological examination. Although not standard of care post-operatively, imaging tests such as computed tomography/magnetic resonance imaging (MRI) were considered if there was a high clinical suspicion of a CSF leak.

End point type	Secondary
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End point timeframe:

Day 0 (Intra-operative) to Day 30 (+/-3 days) post-operative

End point values	Tisseel (PPS)	DuraSeal (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	95		
Units: Participants	8	2		

Statistical analyses

Statistical analysis title	Stats
Comparison groups	DuraSeal (PPS) v Tisseel (PPS)
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
Method	Regression, Logistic
Parameter estimate	Mean difference (net)
Point estimate	-9.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.11
upper limit	2.54

Notes:

[2] - To demonstrate non-inferiority of Tisseel to DuraSeal for the primary endpoint, the lower limit of the 95% CI (based on normal approximation) for the difference in average predicted proportions had to be greater than -10%.

Secondary: Duration in Surgery (minutes)

End point title	Duration in Surgery (minutes)
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End point description:

Patients undergoing elective cranial surgery for the treatment of a pathological condition (e.g., benign/malignant tumours, vascular malformations, or Chiari type 1 malformations) specifically located in the posterior fossa (PF) or supratentorial (ST) regions.

End point type	Secondary
End point timeframe:	
Day 0 (intra-operatively)	

End point values	Tisseel (PPS)	DuraSeal (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	95		
Units: Minutes				
arithmetic mean (standard deviation)	241.8 (\pm 100.80)	210.3 (\pm 90.49)		

Statistical analyses

Statistical analysis title	Stats
Comparison groups	Tisseel (PPS) v DuraSeal (PPS)
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0241
Method	Wilcoxon (Mann-Whitney)

Secondary: Time from Dural Closure (application of IP) until End of Surgery

End point title	Time from Dural Closure (application of IP) until End of Surgery
End point description:	
Suture closure techniques include continuous simple, continuous locked, interrupted.	
End point type	Secondary
End point timeframe:	
Day 0 (Intra-operatively)	

End point values	Tisseel (PPS)	DuraSeal (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	95		
Units: MInutes				
arithmetic mean (standard deviation)	34 (\pm 16.13)	31.4 (\pm 17.07)		

Statistical analyses

Statistical analysis title	Stats
Comparison groups	Tisseel (PPS) v DuraSeal (PPS)
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1015
Method	Wilcoxon (Mann-Whitney)

Secondary: Length of Stay in Hospital (days)

End point title	Length of Stay in Hospital (days)
End point description: Days in hospital calculation is Day 0 - Discharge.	
End point type	Secondary
End point timeframe: Day 0 to Day 60 (Study Completion)	

End point values	Tisseel (PPS)	DuraSeal (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	89	95		
Units: Days				
arithmetic mean (standard deviation)	13.5 (± 15.57)	12.6 (± 8.67)		

Statistical analyses

Statistical analysis title	Stats
Comparison groups	Tisseel (PPS) v DuraSeal (PPS)
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9943
Method	Wilcoxon (Mann-Whitney)

Post-hoc: Number of Surgical Site Infections (SSI)

End point title	Number of Surgical Site Infections (SSI)
End point description: Surgical site infections were evaluated by the surgeon or designated physician according to United States (US) National Healthcare Safety Network (NHSN) criteria as specified in the study protocol.	

End point type	Post-hoc
End point timeframe:	
Day 0 (Intra-operative) to Day 30 (+/-3 days) post-operative	

End point values	Tisseel (SAS)	DuraSeal (SAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	110	114		
Units: SSI				
number (not applicable)	1	4		

Statistical analyses

Statistical analysis title	Stats
Comparison groups	Tisseel (SAS) v DuraSeal (SAS)
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Logistic
Parameter estimate	Mean difference (net)
Point estimate	-5.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.6
upper limit	3.39

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day -30 (Pre-operative) to Day 60 (+/- 3 days)

Adverse event reporting additional description:

Treatment-Emergent Adverse Events (TEAE) were reported for both Adverse Event (AE) and Serious Adverse Events (SAE). TEAE's are events that began or worsen in severity after the first administration of treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18
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Reporting groups

Reporting group title	Tisseel
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Reporting group description: -

Reporting group title	DuraSeal
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Reporting group description: -

Serious adverse events	Tisseel	DuraSeal	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 110 (20.00%)	17 / 114 (14.91%)	
number of deaths (all causes)	3	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Brain Contusion			
subjects affected / exposed	1 / 110 (0.91%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural Haematoma			
subjects affected / exposed	0 / 110 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	0 / 110 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocephalus			

subjects affected / exposed	1 / 110 (0.91%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Haemorrhage			
subjects affected / exposed	0 / 110 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomeningocele			
subjects affected / exposed	0 / 110 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Dehiscence			
subjects affected / exposed	0 / 110 (0.00%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Haematoma			
subjects affected / exposed	1 / 110 (0.91%)	0 / 114 (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 / 110 (0.91%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Brain Oedema			
subjects affected / exposed	1 / 110 (0.91%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal Fluid Leakage			
subjects affected / exposed	7 / 110 (6.36%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	4 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	1 / 110 (0.91%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	3 / 110 (2.73%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic Intracranial Hypertension			
subjects affected / exposed	0 / 110 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensorimotor Disorder			
subjects affected / exposed	0 / 110 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior Sagittal Sinus Thrombosis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic Infarction			
subjects affected / exposed	1 / 110 (0.91%)	0 / 114 (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	1 / 110 (0.91%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Discomfort			
subjects affected / exposed	0 / 110 (0.00%)	1 / 114 (0.88%)	
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			
Aspiration			
subjects affected / exposed	1 / 110 (0.91%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 110 (1.82%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	2 / 110 (1.82%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Distress			
subjects affected / exposed	1 / 110 (0.91%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	2 / 110 (1.82%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 110 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal Insufficiency			

subjects affected / exposed	1 / 110 (0.91%)	0 / 114 (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			
Brain Abscess			
subjects affected / exposed	0 / 110 (0.00%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain Empyema			
subjects affected / exposed	0 / 110 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epidural Empyema			
subjects affected / exposed	0 / 110 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			
subjects affected / exposed	1 / 110 (0.91%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 110 (0.00%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 110 (0.91%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft Tissue Infection			
subjects affected / exposed	0 / 110 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Infection			

subjects affected / exposed	0 / 110 (0.00%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Tisseel	DuraSeal	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 110 (41.82%)	46 / 114 (40.35%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 110 (4.55%)	6 / 114 (5.26%)	
occurrences (all)	5	6	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 110 (5.45%)	3 / 114 (2.63%)	
occurrences (all)	8	4	
Headache			
subjects affected / exposed	20 / 110 (18.18%)	21 / 114 (18.42%)	
occurrences (all)	25	25	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	15 / 110 (13.64%)	15 / 114 (13.16%)	
occurrences (all)	15	16	
Pyrexia			
subjects affected / exposed	3 / 110 (2.73%)	7 / 114 (6.14%)	
occurrences (all)	6	7	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	8 / 110 (7.27%)	5 / 114 (4.39%)	
occurrences (all)	9	5	
Nausea			
subjects affected / exposed	10 / 110 (9.09%)	14 / 114 (12.28%)	
occurrences (all)	12	16	
Vomiting			

subjects affected / exposed	10 / 110 (9.09%)	14 / 114 (12.28%)	
occurrences (all)	15	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported