Clinical trial results:
A Prospective Randomized Controlled Study Evaluating the Safety and Efficacy of EVICEL used for Suture-Line Sealing in Dura-Mater Closure during Paediatric Neurosurgical Cranial Procedures

Summary

EudraCT number	2013-003558-26
Trial protocol	GB
Global end of trial date	17 September 2021

Results information

Result version number	v1
This version publication date	01 April 2022
First version publication date	01 April 2022

Trial information

Trial identification

Sponsor protocol code	BIOS-13-006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02309645
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	04 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 August 2021
Global end of trial reached?	Yes
Global end of trial date	17 September 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of EVICEL® when used for suture-line sealing in dura mater closure in elective paediatric cranial neurosurgery to provide intraoperative watertight closure.

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. 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:

Many cranial neurosurgical procedures require that the surgeon pass through the dura mater to gain access to the neural elements. Despite advances in neurosurgical techniques and the development of new methods to repair dura mater defects, cerebrospinal fluid (CSF) leakage remains one of the challenging complications of cranial surgery. Meticulous repair of the dural incision should achieve intra-operative watertight closure as the first-line protection from postoperative CSF leakage, which may lead to serious complications such as pseudomeningocele, delayed wound healing, CSF fistula, surgical site infection (SSI), and meningitis.

Evidence for comparator:

In cranial neurosurgical procedures (craniotomy or craniectomy) that require dural incision, current techniques to obtain an intra-operative watertight dural closure include (but are not limited to):

- Primary suture closure of the dural incision
- Augmentation or onlay patching of the dural incision with synthetic or tissue-based patches
- Adjunctive use of various products (prophylactically or to treat persistent CSF leak after primary suture closure):
- Additional repair suture
- Synthetic Sealants (e.g., polyethylene glycol,etc)
- Biological Sealants (e.g., fibrin sealants, glutaraldehyde crosslinked bovine albumin)
- Autologous tissue buttresses or duroplasty (e.g., fat, muscle, per cranium, etc.)
- Gelatin pads or other resorbable biomaterials

The study is aligned with EU Guidance on clinical investigation of plasma-derived fibrin sealants (CPMP/BPWG/1089/00, 29 July 2004) by having a control group that received the standard treatment (additional sutures) without fibrin sealant and by ensuring that the clinical situations under study represented those encountered in actual clinical practice.

For subjects not achieving intra-operative watertight closure, the Investigator could revert to their institutional standard of care. This was applicable to both treatment groups.

Actual start date of recruitment	09 October 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
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)	2
Children (2-11 years)	24
Adolescents (12-17 years)	14
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 9th October 2014 and the last subject was recruited on 17th August 2021. The last subject's last visit took place on 17 September 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	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	EVICEL

Arm description: -

Arm type	Experimental
Investigational medicinal product name	EVICEL Solution for Sealant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for sealant
Routes of administration	Other use

Dosage and administration details:

Up to 2 Applications (up to 2 layers per application)

Arm title	Sutures

Arm description: -

Arm type	Additional Sutures
Investigational medicinal product name	Sutures (per Institutional Standard of Care)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Other use

Dosage and administration details:

Additional sutures as required dependent on size of dural defect

Number of subjects in period 1	EVICEL	Sutures
Started	25	15
Completed	25	15

Baseline characteristics

Reporting groups	
Reporting group title	EVICEL
Reporting group description: -	
Reporting group title	Sutures
Reporting group description: -	

Reporting group values	EVICEL	Sutures	Total
Number of subjects	25	15	40
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	1	1	2
Children (2-11 years)	14	10	24
Adolescents (12-17 years)	10	4	14
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	10.0	10.0	
full range (min-max)	0.8 to 17.0	0.6 to 15.0	-
Gender Categorical Units: Subjects			
Female	11	6	17
Male	14	9	23

Subject analysis sets	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: All randomized subjects	
Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description: All subjects in the Full Analysis Set who have no major protocol deviations affecting the primary 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	32	40
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	2	1	2
Children (2-11 years)	24	19	24
Adolescents (12-17 years)	14	12	14
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	10.0	10.0	10.0
full range (min-max)	0.6 to 17.0	0.6 to 17.0	0.6 to 17.0
Gender Categorical Units: Subjects			
Female	17	14	17
Male	23	18	23

End points

End points reporting groups	
Reporting group title	EVICEL
Reporting group description: -	
Reporting group title	Sutures
Reporting group description: -	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: All randomized subjects	
Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description: All subjects in the Full Analysis Set who have no major protocol deviations affecting the primary 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: Proportion of success (intra-operative watertight closure) in the treatment of intra-operative Cerebrospinal Fluid Leakage (CSF) defined as no CSF leakage from dural repair intra-operatively during Valsalva maneuver 20-25 cm H2O for 5-10 seconds

End point title	Proportion of success (intra-operative watertight closure) in the treatment of intra-operative Cerebrospinal Fluid Leakage (CSF) defined as no CSF leakage from dural repair intra-operatively during Valsalva maneuver 20-25 cm H2O for 5-10 seconds
End point description:	
End point type	Primary
End point timeframe: Intra-operative	

End point values	EVICEL	Sutures	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25	15	40	
Units: Participants				
number (not applicable)				
Primary Endpoint Success	23	5	28	

Statistical analyses

Statistical analysis title	Primary Effectiveness Endpoint

Statistical analysis description:

The proportion of successes was summarized descriptively by treatment group. In addition, a two-sided 95% confidence interval (CI) was reported for the ratio of the proportion of success in the EVICEL group and Control group (PE/PC), using the Farrington-Manning score method.

Comparison groups	EVICEL v Sutures
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk ratio (RR)
Point estimate	2.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.53
upper limit	6.16
Variability estimate	Standard error of the mean

Other pre-specified: Incidence of CSF Leakage within 5 (+/-2) Days Post-operatively

End point title	Incidence of CSF Leakage within 5 (+/-2) Days Post-operatively

End point description:

Events of pseudomeningocele, a manifestation of CSF leak, are reported in the Serious Adverse Event table

End point type	Other pre-specified

End point timeframe:

5 (+/-2) Days Post-operatively

End point values	EVICEL	Sutures		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	15		
Units: Participants	0	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Incidence of CSF Leakage Between 5 Days and 30 Days Post-operatively

End point title	Incidence of CSF Leakage Between 5 Days and 30 Days Post-operatively

End point description:

Events of pseudomeningocele, a manifestation of CSF leak, are reported in the Serious Adverse Event table

End point type	Other pre-specified

End point timeframe:
Between 5 (+/-2) Days and 30 (+/-3) Days Post-operatively

End point values	EVICEL	Sutures		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	15		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Incidence of Surgical Site Infections

End point title	Incidence of Surgical Site Infections

End point description:
Incidence of Post-operative SSI according to National Healthcare Safety Network

End point type	Other pre-specified

End point timeframe:
Immediately post-operative period up to 30 (+/-3) days post-operatively

End point values	EVICEL	Sutures		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	15		
Units: Participants	1	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinically Significant Changes - Laboratory Tests

End point title	Clinically Significant Changes - Laboratory Tests

End point description:
Abnormal changes to laboratory results considered clinically significant by Investigator

End point type	Other pre-specified

End point timeframe:
Baseline (within 24 hours of surgery) to 5 (+/-2) Days Post-operatively

End point values	EVICEL	Sutures		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	15		
Units: Subjects	0	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From time of randomization up to and including the 30 (+/-3) Day 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 AE.

Relationship to treatment was conducted for the study product arm only.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	EVICEL
Reporting group description: -	
Reporting group title	Sutures

Reporting group description: -

Serious adverse events	EVICEL	Sutures	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 26 (19.23%)	8 / 14 (57.14%)	
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)			
Medulloblastoma recurrent			
subjects affected / exposed	1 / 26 (3.85%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural haematoma			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomeningocele	Additional description: 1 event in EVICEL group up-graded by Sponsor; Causality assessment not required for Suture group		

subjects affected / exposed	1 / 26 (3.85%)	4 / 14 (28.57%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Neurofibromatosis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 26 (3.85%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 26 (3.85%)	2 / 14 (14.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocephalus			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Transverse sinus thrombosis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Haemorrhagic cyst			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	1 / 26 (3.85%)	0 / 14 (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			
Meningitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 14 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
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: 5 %

Non-serious adverse events	EVICEL	Sutures	
Total subjects affected by non-serious adverse events subjects affected / exposed	22 / 26 (84.62%)	13 / 14 (92.86%)	
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	2 / 14 (14.29%) 2	
General disorders and administration site conditions Catheter site pain subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 14 (7.14%) 1	
Catheter site related reaction subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 14 (7.14%) 1	
Fatigue subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 14 (0.00%) 0	
Implant site effusion subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 14 (7.14%) 1	
Pain subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	2 / 14 (14.29%) 2	
Pyrexia subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	5 / 14 (35.71%) 8	
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 14 (7.14%) 1	
Reproductive system and breast disorders Scrotal swelling subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 14 (7.14%) 1	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 26 (7.69%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Productive cough			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Investigations			
Blood pressure diastolic decreased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Haemoglobin decreased			
subjects affected / exposed	1 / 26 (3.85%)	2 / 14 (14.29%)	
occurrences (all)	1	2	
Oxygen saturation decreased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Post procedural constipation			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Post procedural haematoma			
subjects affected / exposed	1 / 26 (3.85%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Post procedural swelling			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Postoperative wound complication			
subjects affected / exposed	1 / 26 (3.85%)	1 / 14 (7.14%)	
occurrences (all)	1	1	

Procedural nausea			
subjects affected / exposed	1 / 26 (3.85%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Procedural pain			
subjects affected / exposed	6 / 26 (23.08%)	3 / 14 (21.43%)	
occurrences (all)	6	4	
Procedural vomiting			
subjects affected / exposed	2 / 26 (7.69%)	1 / 14 (7.14%)	
occurrences (all)	2	1	
Wound complication			
subjects affected / exposed	2 / 26 (7.69%)	2 / 14 (14.29%)	
occurrences (all)	2	2	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	2 / 26 (7.69%)	1 / 14 (7.14%)	
occurrences (all)	2	2	
Dilation ventricular			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Tachycardia NOS			
subjects affected / exposed	2 / 26 (7.69%)	3 / 14 (21.43%)	
occurrences (all)	2	3	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 26 (34.62%)	5 / 14 (35.71%)	
occurrences (all)	11	6	
Hemiparesis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Dysaesthesia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
IIIrd nerve paralysis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Paraesthesia			

subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Sensory loss			
subjects affected / exposed	0 / 26 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Hemiplegia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Eye disorders			
Conjunctivitis, unspecified			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Diplopia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Eye swelling			
subjects affected / exposed	4 / 26 (15.38%)	4 / 14 (28.57%)	
occurrences (all)	4	4	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 26 (3.85%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	1 / 26 (3.85%)	3 / 14 (21.43%)	
occurrences (all)	1	4	
Diarrhoea			
subjects affected / exposed	1 / 26 (3.85%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Dysphagia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Nausea			

subjects affected / exposed	5 / 26 (19.23%)	4 / 14 (28.57%)	
occurrences (all)	5	4	
Vomiting			
subjects affected / exposed	12 / 26 (46.15%)	6 / 14 (42.86%)	
occurrences (all)	14	9	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 26 (0.00%)	2 / 14 (14.29%)	
occurrences (all)	0	2	
Pruritus generalized			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Swelling face			
subjects affected / exposed	1 / 26 (3.85%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 26 (3.85%)	1 / 14 (7.14%)	
occurrences (all)	1	1	
Neck pain			
subjects affected / exposed	3 / 26 (11.54%)	0 / 14 (0.00%)	
occurrences (all)	3	0	
Muscular weakness			
subjects affected / exposed	2 / 26 (7.69%)	1 / 14 (7.14%)	
occurrences (all)	3	1	
Pain in extremity			
subjects affected / exposed	3 / 26 (11.54%)	0 / 14 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Rhinitis			

subjects affected / exposed	2 / 26 (7.69%)	0 / 14 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Fluid overload			
subjects affected / exposed	0 / 26 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2018	Amendment was primarily to update the timeline requirement for adverse events to be reported to the sponsor.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported