



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 | v2 (current) |
| This version publication date | 03 November 2022 |
| First version publication date | 01 April 2022 |
| Version creation reason | |

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) | 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 | 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 | Sutures v EVICEL |
| 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 | Sutures |
|-----------------------|---------|

Reporting group description: -

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

Reporting group description: -

| Serious adverse events | Sutures | EVICEL | |
|---|---|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 14 (57.14%) | 5 / 26 (19.23%) | |
| 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 | 0 / 14 (0.00%) | 1 / 26 (3.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Post procedural haematoma | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| 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 | 4 / 14 (28.57%) | 1 / 26 (3.85%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Neurofibromatosis | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 26 (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 | | | |
| Cerebrospinal fluid leakage | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 26 (3.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrocephalus | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 1 / 26 (3.85%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Partial seizures | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocephalus | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|----------------|----------------|--|
| Transverse sinus thrombosis subjects affected / exposed | 1 / 14 (7.14%) | 0 / 26 (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 | | | |
| Haemorrhagic cyst subjects affected / exposed | 1 / 14 (7.14%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia subjects affected / exposed | 0 / 14 (0.00%) | 1 / 26 (3.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Vomiting subjects affected / exposed | 1 / 14 (7.14%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Diabetes insipidus subjects affected / exposed | 0 / 14 (0.00%) | 1 / 26 (3.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Meningitis subjects affected / exposed | 0 / 14 (0.00%) | 1 / 26 (3.85%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shunt infection subjects affected / exposed | 1 / 14 (7.14%) | 0 / 26 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

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

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

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

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

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

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