Amsterdam, 23rd June 2022
EMA/577885/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Evicel

International non-proprietary name: Human thrombin / Human Fibrinogen

Procedure no.: EMA/H/C/000898/P46/0030

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

On 15 March 2022, the MAH submitted a completed paediatric study for Evicel, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The submission concerns a clinical study titled "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", Protocol BIOS-13-006 which was conducted as part of a Paediatric Investigation Plan, EMEA-001149-PIP01-11-M07 (EMA Decision P/0397/2021, PIP Study 5). This clinical study was completed on September 17, 2021 (Last Patient Last Visit). Pursuant to Article 46 of Regulation (EC) 1901/2006, the Clinical Study Report (CSR) summarizing the study outcome is submitted as Article 46 PAM.

The MAH is not proposing any changes to EVICEL's Product Information following completion of study BIOS-13-006.

2.2. Information on the pharmaceutical formulation used in the study

EVICEL is a human plasma-derived fibrin sealant consisting of two components: Human clottable protein containing mainly fibrinogen and fibronectin and Human Thrombin. It is administered to the surgical site by spraying or dripping with a single-use applicator device.

2.3. Clinical aspects

2.3.1. Introduction

EVICEL is a human plasma-derived fibrin sealant consisting of two components, mainly human fibrinogen/fibronectin, and Human Thrombin. EVICEL is administered by spraying or dripping with a single-use applicator device.

EVICEL was approved in the EU via the Centralized Procedure in October 2008 for 1 mL, 2 mL, and 5 mL kit, respectively. EVICEL is indicated for use in adults as a supportive treatment in surgery where standard surgical techniques were insufficient, for improvement of hemostasis. EVICEL is also indicated in adults as suture support for hemostasis in vascular surgery and for suture-line sealing in dura-mater closure.

Predecessor product contained the clot-stabilizing agent tranexamic acid (TA). As in vivo studies revealed that direct application of fibrin sealant containing TA to cortex and spinal cord may cause generalized seizures, and exhibit direct effects on neuronal cells predecessor product was contraindicated for use in neurosurgery, and EVICEL was developed without TA to enable use in neurosurgery and surgical procedures where contact with CSF or dura-mater can occur.

Safety and effectiveness of EVICEL for use as an adjunct to sutured dural repair to provide intra-operative watertight closure has been evaluated in (Study 400-09-001). This study demonstrated that EVICEL was safe and effective as an adjunct to primary dural sutures in adults to provide watertight closure of the dura mater and that it was superior to suture repair. Results of this study were submitted to the EMA and approved as a basis for indication for suture line sealing in dura mater closure in 2013.

Following the requirements of EU Paediatric Regulation (EC) No 1901/2006, a clinical study in the paediatric population was conducted in a similar surgical setting to the adult neurosurgical indication. The clinical trial summarized in this report was conducted as part of the EU Paediatric Investigation Plan (PIP) (EMEA-001149-PIP01-11-M07) and UK Paediatric Investigation Plan (MHRA-100083-PIP01-21-M01 adopted post-Brexit).

2.3.2. Clinical study

Clinical study number and title

Study Number: BIOS-13-006, Phase III-study

Title: "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"

Clinical Trial Registration: NCT02309645; EudraCT Number: 2013-003558-26

Description

This was a prospective randomized, open-label, multi-center-controlled study evaluating the effectiveness of EVICEL as an adjunct to sutured dural closure compared to control (sutures) to obtain an intra-operative watertight dural closure during neurosurgical procedures.

Paediatric subjects, undergoing elective or urgent craniotomy/craniectomy for pathological processes (such as benign or malignant tumors, vascular malformations, and Chiari 1 malformations) in the posterior fossa or in the supra-tentorial region and who were demonstrated to have spontaneous or after Valsalva maneuver cerebrospinal fluid (CSF) leakage following a primary attempt at suture closure of the dural incision.

Methods

Study participants

First subject randomized: 09 October 2014, Last subject completed: 17 September 2021

Newborn infants (birth to 27 days, including pre-term newborn infants born ≤37 weeks gestation, Infants and toddlers (28 days to <24 months), Children (2 to 11 years), Adolescents (12 to <18 years).

Main inclusion criteria:

- Patient undergoing elective or urgent craniotomy/craniectomy for pathological processes (such as benign or malignant tumors, vascular malformation, and Chiari 1 malformations) in the posterior fossa or in the supratentorial region and who are demonstrated to have persistent CSF leakage following primary attempt at suture closure of the dural incision.

- Patients who are less than 18 years of age.

- Surgical wound classification Class I (Protocol Appendix II). Penetration of mastoid air cells during partial mastoidectomy is permitted.

- The cuff of native dura along the craniotomy edge on each side is wide enough based on surgeon's judgment to facilitate suturing and to allow for sufficient surface area for adherence of the investigational product.

Main exclusion criteria:

- Subjects with a dura lesion from a recent surgery that still has the potential for CSF leakage.

- Hydrocephalus (occlusive hydrocephalus is permitted when caused by posterior fossa pathology to be treated, i.e., hydrocephalus is due to blockage caused by a tumor to be removed).

- Existing CSF (ventricular, etc.) drains, shunts, Cushing/Dandy cannulation, or burr holes which damage the dura.

- Dura injury during craniotomy/craniectomy that cannot be eliminated by widening the craniotomy/craniectomy to recreate the native dura cuff.

- Use of implants made of synthetic materials coming into direct contact with dura (e.g., polytetrafluoroethylene (PTFE) patches, shunts, ventricular and subdural drains).

- Placement of Gliadel Wafers.

- Persistent signs of increased brain turgor.

- Patient has a gap between durotomy edges of greater than 2 mm after primary dural closure.

- Intersecting durotomy scars in the surgical path from a previous operation that cannot be completely removed by the planned dura resection.

- Two or more separate dura defects, including defects from ventricular cannulation and ventricular-peritoneal shunting.

Treatments

EVICEL is a human plasma-derived fibrin sealant. EVICEL consists of two components: 1) Biologically Active Component 2 (BAC2), a concentrate of human clottable protein containing mainly fibrinogen and fibronectin and 2) Human Thrombin. Application can be made by dripping or spraying in accordance with the EVICEL Investigator Brochure, Accessory Tip Directions, and Device and Pressure Regulator Instructions for use.

For each subject, at least 1 kit of EVICEL was thawed and available for administration prior to randomization. Randomization took take place following completion of the primary sutured dural repair and closure was evaluated for intra-operative CSF leakage.

If a spontaneous leak was not present following primary suture repair, the closure was tested with a baseline Valsalva maneuver (20-25 cm H2O for 5-10 seconds). Only subjects with a CSF leak (spontaneous or upon Valsalva maneuver) were randomized into the study.

For subjects randomized to receive EVICEL, a thin layer of EVICEL was applied immediately following randomization to the entire length of the dural suture line and the adjacent area to at least 5 mm away, including all suture holes. If necessary, a second layer of EVICEL could be applied. A cure time 1-2 minutes was to be allotted between layers to allow for polymerization. CSF leakage was evaluated with a Valsalva maneuver 20-25 cm H2O for 5-10 seconds.

If CSF leakage was still apparent, a second treatment (up to 2 layers) with EVICEL could be applied. CSF leakage was re-evaluated with a second Valsalva maneuver 20-25 cm H2O for 5-10 seconds.

- If watertight closure was not evident after this final Valsalva maneuver, the subject was deemed a failure and the surgeon could revert to their standard of care for closure including the use of other commercially available fibrin sealants (except EVICEL) or an onlay dural patch.
- If watertight closure was achieved, no further treatment, including the use of onlays, was allowed.

Closure of the remaining layers of the surgical site was performed according to the surgeon’s standard of practice.

Subjects randomized to Control (Additional Sutures) received additional dural repair sutures applied immediately following randomization as deemed necessary by the surgeon. The CSF leakage was to be evaluated with the Valsalva maneuver at 20-25 cm H2O pressure for 5-10 seconds.

- If watertight closure was not evident after the Valsalva maneuver, the subject was deemed a failure and the surgeon could revert to their standard of care for closure including the use of other commercially available fibrin sealants (except EVICEL) or an onlay dural patch.
- If watertight closure was achieved but the surgeon felt that an adjunct (excluding the use of fibrin sealants) was required to assure durability of closure, then such treatment could be applied. This was considered a treatment success.

Closure of the remaining layers of the surgical site was performed according to the surgeon's standard of practice.

Objective(s)

To evaluate the safety and efficacy of EVICEL Solutions for sealant (EVICEL) as an adjunct when used for suture-line sealing in dura-mater closure in paediatric cranial neurosurgery to provide intra-operative watertight closure.

Outcomes/endpoints

Subjects were followed post-operatively through discharge and for 30 days (±3 days) post-surgery. The incidence of CSF leaks was assessed at 5 days (±2 days) and 30 days (±3 days) post-operatively as detected by any of the following: clinical observation, diagnostic testing, or the need for surgical intervention to treat a CSF leak or pseudomeningocele.

The primary endpoint was the proportion of success (intra-operative watertight closure) in the treatment of intra- operative CSF leakage define as no CSF leakage from dural repair intra-operatively, during Valsalva maneuver 20-25 cm H2O for 5-10 seconds.

The following safety and tolerability variables were included in this study*:*

- Incidence of CSF leakage within 5 days (±2 days) post-operatively
- Incidence of CSF leakage within 30 days (±3 days) post-operatively
- Incidence of adverse events
- Laboratory tests
- Incidence of surgical site infections (SSI) according to National Healthcare Safety Network (NHSN) criteria within 30 days (±3 days) post-operatively.

Sample size

Forty-two (42) paediatric subjects with intra-operative CSF leak following primary suturing of the dura were planned to be stratified by surgical procedure, posterior fossa or supratentorial, and planned to be randomized in a 2:1 allocation ratio to either EVICEL arm or additional sutures (control arm).

Statistical Methods, Randomisation

Analysis Sets

The following three analysis sets were defined:

- The Safety set consists of all subjects who received treatment.
- The Full Analysis Set (FAS) consists of all randomized subjects (equivalent to the Intent-to-Treat [ITT] set).
- The Per-Protocol (PP) set consists of all FAS subjects who have no major protocol deviations affecting the primary endpoint.

The primary effectiveness endpoint was analyzed using the FAS and the PP set. However, the primary analysis was based on the FAS. The PP analysis was considered confirmatory.

In all cases, treatment allocation was based on randomization for the primary effectiveness endpoint using the FAS. If more than 2 subjects were to be mis-randomized, then an additional confirmatory analysis based on treatment received was to be performed for the primary effectiveness endpoint, using the FAS.

Effectiveness Variables:

For the effectiveness endpoint, the proportion of successes was summarized descriptively by treatment group. In addition, two-sided 95% confidence intervals (CIs) were reported for the ratio of the proportion of success in the EVICEL group/proportion of success in Control group (PE/PC), using the Farrington-Manning score method.

Safety Variables:

All safety/secondary variables were summarized descriptively for 5-day (±2 days) and 30-day (±3 days) visits using the Safety set. No inferential statistical analysis was carried out.

All Adverse Events (AEs) were summarized descriptively by treatment received, using Medical Dictionary for Regulatory Activities (MedDRA) terminology. Laboratory values are reported in SI units. Values and changes from baseline were listed, but not summarized.

Results

Participant flow

This study was conducted as part of EU and UK Paediatric Investigation Plan (PIPs); a minimum of 40 subjects in 2:1 randomization was required to be enrolled per the PIP. The number of randomized subjects planned for this trial was 42 subjects to allow for 2:1 ratio. The study was closed after meeting the PIP requirement of 40 subjects enrolled. A total of 25 subjects were randomized to EVICEL and 15 subjects to additional sutures from 7 centers in the UK.

Analysis Sets

A total of 40 subjects recruited at 7 centers in the UK were randomized into this study, with 25 subjects in the EVICEL group and 15 subjects in the Sutures group. All subjects completed the study as planned.

The FAS (ITT set) consisted of 25 subjects (100.0%) randomized to EVICEL and 15 subjects (100.0%) randomized to Sutures. In the FAS, the Sutures group consisted of 14 subjects treated with Sutures

alone and 1 subject (22202) that was randomized to Sutures but received EVICEL. This subject was analyzed in the Sutures group for ITT set and in the EVICEL group for the Safety set. Therefore, the Safety set consisted of 26 EVICEL subjects and 14 Sutures subjects. The PP set consisted of 22 EVICEL subjects (88.0%) and 10 subjects (66.7%) randomized to Sutures.

Demographics

The study population had a mean (standard deviation [sd]) age of 9.7 (4.4) years in EVICEL group and 9.2 (4.3) years in Sutures group, and consisted of more males in the EVICEL group (56.0%) than in Sutures group (60.0%). Subjects included in the study ranged from 7 months to 17 years of age, with a median of 10 years in both groups. Overall, 30% of subjects had previous surgery, no subject had a history of superficial vein thrombosis (SVT) or deep vein thrombosis/pulmonary embolism (DVT/PE), and no subject had a family history of DVT/PE. Overall, 22.5% had never smoked, while, for 70.0%, this was not relevant due to patient age.

Surgical Indication and Approach

Overall, the most common indication for surgery was tumor (65.0%), followed by epilepsy (17.5%), arteriovenous (A-V) malformation (7.5%), "other" conditions (5.0%), arachnoid cyst 2.5%, and Chiari malformation (2.5%). Overall 97.5% of subjects underwent a craniotomy and 2.5% underwent a craniectomy. Supratentorial approach was used in 82.5% of the subjects, and a posterior fossa approach was used in 17.5%.

Treatment Groups

The distribution of the operative procedure and the type of approach was similar in the two treatment groups: 96.0% of subjects in the EVICEL group and 100.0% subjects in the Sutures group underwent craniotomy, while 84.0% of the subjects in EVICEL group and 80.0% of the subjects in Sutures group underwent a supratentorial approach.

Operative Parameters

As per protocol, all subjects had a documented CSF leak prior to randomization. Overall, 24 subjects (60.0%) had spontaneous CSF leak, whereas in 15 subjects (93.8%) a CSF leak was detected after performing a Valsalva maneuver. In the EVICEL group, 14 subjects (56.0%) had a spontaneous CSF leak and, of the 11 subjects with no spontaneous CSF leak and in whom a Valsalva maneuver was performed, 11 subjects (100.0%) had a CSF leak after the Valsalva maneuver. In the Sutures group, 10 subjects (66.7%) had a spontaneous CSF leak and, of the 5 subjects with no spontaneous CSF leak, 4 subjects (80.0%) had a CSF leak after the Valsalva maneuver was performed.

The operative parameters relating to the duration of surgery and hospitalization were similar in the 2 treatment groups. The median duration of surgery and median time in operating room were 305 minutes and 376 minutes, respectively, for EVICEL, and 288 minutes and 361 minutes, respectively, for Sutures.

In twenty-three of the twenty-five subjects in the EVICEL treatment group (92.0%), 1 EVICEL kit was used, while in two subjects (8.0%), a second EVICEL kit was used. The median amount of EVICEL used in the subjects was 4.0 mL (range 2.0-8.0 mL). For the 14 subjects who received sutures, the median number of sutures used was 2.0 (1.0, 12.0).

Efficacy results

Primary effectiveness analysis

The primary endpoint was the proportion of success (intra-operative watertight closure) in the treatment of intra-operative CSF leakage defined as no CSF leakage from the sutured dural repair intra-operatively, during Valsalva maneuver at 20-25 cm H2O pressure for 5-10 seconds.

The primary effectiveness analysis was based on the full analysis set. Overall, in the FAS, 23 of 25 EVICEL subjects, and 5 of 15 Suture subjects were considered a success, constituting success rates of 92.0% for EVICEL and 33.3% for Sutures. Two (2) subjects in the EVICEL group and 10 subjects in the Sutures group were considered failures. The proportion of subjects with primary endpoint successes was higher in EVICEL group (92.0%) compared with Sutures group (33.3%); the ratio of proportions (EVICEL/Sutures) was 2.76 (95% CI: 1.53-6.16).

Within the posterior fossa stratum, 2/4 EVICEL subjects and 0/3 Sutures subjects were considered a success, constituting success rates of 50.0% and 0.0%, respectively. Within the supratentorial stratum, 21/21 EVICEL subjects and 5/12 Sutures subjects were considered a success, constituting success rates of 100.0% for EVICEL and 41.7% for Sutures.

Supportive analysis

The supportive analysis (PP set) shows similar results in EVICEL group, with a success rate of 90.9% (20 of 22 subjects), and higher success rate for Sutures group (40.0% [4 of 10 subjects]). The ratio of proportions (EVICEL/Sutures) was 2.27 (95% CI: 1.27-5.53). The primary effectiveness endpoint was also analyzed using the Safety set. Overall, 23 of 26 subjects (88.5%) in the EVICEL group and 5 of 14 subjects (35.7%) in the Sutures group were considered successes.

Intra-operative analysis

Analyses of intra-operative parameters (FAS) showed that, in the EVICEL group, most subjects (92.0%) were treated with 1 application of EVICEL. The majority of subjects received 1 layer of EVICEL, and most of the subjects had no CSF leak following EVICEL application and the final Valsalva maneuver. For the first EVICEL application, 18 subjects (72.0%) received 1 layer and 7 subjects (28.0%) received 2 layers of EVICEL. A spontaneous leak after EVICEL application was observed in 1 subject (4.0%). A second EVICEL application was documented in 2 subjects (8.0%). For the second EVICEL application, 1 subject (50.0%) received 1 layer and 1 subject (50.0%) received 2 layers. A spontaneous CSF leak was observed in 1 subject (50.0%) after the second application.

Method of application

The most frequently used method of application for EVICEL was via dripping. For EVICEL, a 4-cm control tip was used in 64.0% of the subjects for the first application. A 6-cm yellow flexible tip was used in 32.0% of subjects for the first application and in both of the 2 subjects (100.0%) for the second application.

Watertight closure

Following treatment, watertight closure was obtained for 23 of 25 subjects in the EVICEL group (92.0%), and 5 of 15 subjects in the Sutures group (33.3%); 2 EVICEL subjects and 10 Suture subjects did not have watertight closure after treatment. Of the 10 subjects in the Sutures group that did not have watertight closure, 1 subject was randomized to receive Sutures but instead received EVICEL.

Rescue therapy

Overall, rescue therapy was administered to 12 subjects (30.0%), from which 2 subjects were in the EVICEL group (8.0%) and 10 subjects were in the Sutures group (66.7%). These 12 subjects were all considered primary endpoint failures because of an intra-operative CSF leak following final Valsalva maneuver. Two (2) subjects in the Sutures group received additional treatment to assure durability of

closure. For 1 of these subjects, it was subsequently confirmed following database lock that the additional treatment was a rescue treatment rather than for durability.

Safety results

A total of 118 AEs (of which 7 were considered serious) occurred in the EVICEL group and 110 AEs (of which 16 were considered serious) were reported in the Sutures group. The incidence of subjects who experienced at least 1 AE was 84.6% in the EVICEL group and 100.0% in the Sutures group. The most frequent AEs in both treatment groups were vomiting, followed by headache. The incidence of subjects who experienced at least 1 SAE was 19.2% in the EVICEL group and 57.1% in the Sutures group. Overall, the most frequently occurring SAE was pseudomeningocele which occurred in 5/40 subjects (12.5%) followed by hydrocephalus which occurred in 3/40 subjects (7.5%). All SAEs in the EVICEL group were single occurrences.

Causality assessment to the product was performed for the EVICEL group only. There were no AEs or serious adverse events (SAEs) considered by the investigator as related or possibly related to EVICEL. The sponsor considered 1 SAE (pseudomeningocele) in the EVICEL group to be possibly related to study product. Justification was the possibility that this SAE could have been due to a lack of expected efficacy of EVICEL.

There were no deaths in either group during the study.

In the EVICEL group, at the 5-day visit, CSF leak status was wound healing impaired, without CSF leak for 3 subjects (11.5%). In the Sutures group, at the 5-day visit, CSF leak status was wound healing impaired, with CSF leak for 1 subject (7.1%) and wound healing impaired, without CSF leak for 2 subjects (14.3%). Pseudomeningocele was experienced by 5/40 subjects (12.5%) overall (EVICEL group 1/26 [3.8%], Sutures group 4/14 [28.6%]) at the 5-day visit. At the 30-day visit, the wound healing assessment was considered normal. There was no CSF leak reported between the 5 day and at 30-day follow up visits for all subjects in either of the treatment groups (100.0%). Pseudomeningocele was experienced by 2 subjects (14.3%) in Sutures group and none of the subjects (0.0%) in the EVICEL group at the 30-day visit.

AEs occurring in >= 5% of Subjects in at Least 1 Treatment Group (Safety Set) are displayed in the Table, below:

Table: AEs Occurring in >= 5% of Subjects in at Least 1 Treatment Group (Safety Set)

		EVICEL (N=26)		**Sutures (N=14)**		**Total (N=40)**	
System Organ Class	**Preferred Term**	**Number of Events**	**Number of Subjects (%)**	**Number of Events**	**Number of Subjects (%)**	**Number of Events**	**Number of Subjects (%)**
Cardiac disorders	Bradycardia	2	2 (7.7%)	2	1 (7.1%)	4	3 (7.5%)
	Dilatation ventricular	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Tachycardia	2	2 (7.7%)	3	3 (21.4%)	5	5 (12.5%)
Congenital, familial, and genetic disorders	Neurofibromatosis	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)

		EVICEL (N=26)		Sutures (N=14)		Total (N=40)	
System Organ Class	**Preferred Term**	**Number of Events**	**Number of Subjects (%)**	**Number of Events**	**Number of Subjects (%)**	**Number of Events**	**Number of Subjects (%)**
Eye disorders	Eye Swelling	4	4 (15.4%)	4	4 (28.6%)	8	8 (20.0%)
	Conjunctivitis	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Diplopia	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
Gastrointestinal disorders	Nausea	5	5 (19.2%)	4	4 (28.6%)	9	9 (22.5%)
	Vomiting	14	12 (46.2%)	10	7 (50.0%)	24	19 (47.5%)
	Abdominal pain	1	1 (3.8%)	1	1 (7.1%)	2	2 (5.0%)
	Constipation	1	1 (3.8%)	4	3 (21.4%)	5	4 (10.0%)
	Diarrhoea	1	1 (3.8%)	1	1 (7.1%)	2	2 (5.0%)
	Dysphagia	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
General disorders and administration site conditions	Pyrexia	2	2 (7.7%)	8	5 (35.7%)	10	7 (17.5%)
	Catheter site pain	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Catheter site related reaction	1	1 (3.8%)	1	1 (7.1%)	2	2 (5.0%)
	Fatigue	2	2 (7.7%)	0	0 (0.0%)	2	2 (5.0%)
	Haemorrhagic cyst	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Implant site effusion	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Pain	1	1 (3.8%)	2	2 (14.3%)	3	3 (7.5%)
Immune system disorders	Drug hypersensitivity	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
Infections and infestations	Herpes zoster	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Rhinitis	2	2 (7.7%)	0	0 (0.0%)	2	2 (5.0%)
	Shunt infection	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Urinary tract infection	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)

		EVICEL (N=26)		Sutures (N=14)		Total (N=40)	
System Organ Class	**Preferred Term**	**Number of Events**	**Number of Subjects (%)**	**Number of Events**	**Number of Subjects (%)**	**Number of Events**	**Number of Subjects (%)**
Injury, poisoning and procedural complications	Procedural pain	6	6 (23.1%)	4	3 (21.4%)	10	9 (22.5%)
	Pseudomeningocele	1	1 (3.8%)	4	4 (28.6%)	5	5 (12.5%)
	Post procedural constipation	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Post procedural haematoma	1	1 (3.8%)	1	1 (7.1%)	2	2 (5.0%)
	Post procedural swelling	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Postoperative wound complication	1	1 (3.8%)	1	1 (7.1%)	2	2 (5.0%)
	Procedural nausea	1	1 (3.8%)	1	1 (7.1%)	2	2 (5.0%)
	Procedural vomiting	2	2 (7.7%)	1	1 (7.1%)	3	3 (7.5%)
	Subdural haematoma	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Wound complication	2	2 (7.7%)	2	2 (14.3%)	4	4 (10.0%)
Investigations	Blood pressure diastolic decreased	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Haemoglobin decreased	1	1 (3.8%)	2	2 (14.3%)	3	3 (7.5%)
	Oxygen saturation decreased	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
Metabolism and nutrition disorders	Decreased appetite	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Fluid overload	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
Musculoskeletal and connective tissue disorders	Back pain	1	1 (3.8%)	1	1 (7.1%)	2	2 (5.0%)
	Muscular weakness	3	2 (7.7%)	1	1 (7.1%)	4	3 (7.5%)
	Musculoskeletal stiffness	0	0 (0.0%)	2	2 (14.3%)	2	2 (5.0%)

		EVICEL (N=26)		Sutures (N=14)		Total (N=40)	
System Organ Class	**Preferred Term**	**Number of Events**	**Number of Subjects (%)**	**Number of Events**	**Number of Subjects (%)**	**Number of Events**	**Number of Subjects (%)**
	Neck pain	3	3 (11.5%)	0	0 (0.0%)	3	3 (7.5%)
	Pain in extremity	3	3 (11.5%)	0	0 (0.0%)	3	3 (7.5%)
Nervous system disorders	Cerebrospinal fluid leakage	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	DySAEsthesia	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Headache	11	9 (34.6%)	6	5 (35.7%)	17	14 (35.0%)
	Hemiparesis	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Hemiplegia	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Hydrocephalus	1	1 (3.8%)	2	2 (14.3%)	3	3 (7.5%)
	IIIrd nerve paralysis	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Paraesthesia	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Partial seizures	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Pneumocephalus	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Sensory loss	0	0 (0.0%)	2	2 (14.3%)	2	2 (5.0%)
	Syncope	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Transverse sinus thrombosis	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
Psychiatric disorders	Confusional state	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
Reproductive system and breast disorders	Scrotal swelling	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
Respiratory, thoracic and mediastinal disorders	Cough	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Oropharyngeal pain	2	2 (7.7%)	0	0 (0.0%)	2	2 (5.0%)
	Productive cough	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
Skin and subcutaneous tissue disorders	Pruritus	0	0 (0.0%)	2	2 (14.3%)	2	2 (5.0%)
	Pruritus generalised	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)
	Rash	0	0 (0.0%)	1	1 (7.1%)	1	1 (2.5%)

		EVICEL (N=26)		Sutures (N=14)		Total (N=40)	
System Organ Class	**Preferred Term**	**Number of Events**	**Number of Subjects (%)**	**Number of Events**	**Number of Subjects (%)**	**Number of Events**	**Number of Subjects (%)**
	Swelling face	1	1 (3.8%)	1	1 (7.1%)	2	2 (5.0%)
Vascular disorders	Hypotension	1	1 (3.8%)	2	2 (14.3%)	3	3 (7.5%)

2.3.3. Discussion on clinical aspects

40 Paediatric subjects with pathological processes (such as benign or malignant tumors, vascular malformations, and Chiari 1 malformations) in the posterior fossa or in the supra-tentorial region, underwent elective or urgent craniotomy/craniectomy. Those who were demonstrated to have spontaneous cerebrospinal fluid (CSF) leakage or leakage after Valsalva maneuver following a primary attempt of dural suture closure were treated either with one or two Evicel-layers ("Evicel") or with additional suture repair ("Sutures").

Study design with active control by additional sutures is considered to follow the suggestions of the currently active Clinical Guideline.

Demographic parameters for both treatment groups were similar. The median age was 10 years in both Evicel and Suture groups (overall range was 7 months to 17 years).

Distribution of the operative procedures was similar in both treatment groups.

Intraoperative treatment success (watertight closure) was achieved in overall 23 of 25 (92%) Evicel-subjects, and in 5 of 15 (33%) Sutures-subjects. Further, in posterior-fossa location, success was demonstrated in 2 of 4 (50%) Evicel-subjects, and in 0 of 3 (0%) sutures-subjects. Supportive analyses were also in favour of Evicel. These efficacy results, based on a meaningful study-design, are considered to be convincing.

Viral safety and immunogenicity have not been addressed in this study. However, this is considered to be acceptable due to the long-term post-marketing experience of the medicinal product.

One event of transverse sinus thrombosis was documented in a subject within the sutures-group. No other thromboses or thromboembolic events occurred.

Pruritus, rash or hypersensitivity did not occur in the Evicel-group. "Eye-swelling" (4 respective AEs in each treatment group) and "Swelling face" (1 respective AE in each treatment group) are interpreted in the context of the operation procedure.

Pattern of Adverse Events is continuously in favour of Evicel-treatment. The AE-pattern, overall, corresponds with the neurosurgical intervention and respective events. Of note, even the non-specific listing of events documents favourable or superior safety-pattern for the Evicel subjects.

Documentation of Evicel-use in children in a controlled clinical study setting is acknowledged, specifically in the light of limited data in this patient population.

Overall, the study documents safe and effective use of Evicel in the paediatric population. Controlled design and clearly favourable efficacy and safety results support an indication for suture support in dura mater closure ("neurosurgery") in children.

3. CHMP overall conclusion and recommendation

EVICEL is a human plasma-derived fibrin sealant consisting of two components, mainly human fibrinogen/fibronectin, and Human Thrombin but without potentially neurotoxic tranexamic acid. EVICEL is administered by spraying or dripping as a supportive treatment in surgery, including suture-line sealing in dura-mater closure.

EVICEL was approved in the EU in October 2008.

Safety and effectiveness of EVICEL for use as an adjunct to sutured dural repair to provide intra-operative watertight closure has been demonstrated (Study 400-09-001) to be superior to suture repair in adults. Similar surgical setting in the paediatric population (study BIOS-13-006) as part of the EU Paediatric Investigation Plan (PIP) (EMEA-001149-PIP01-11-M07) and UK Paediatric Investigation Plan (MHRA-100083-PIP01-21-M01 adopted post-Brexit) is reported within this current procedure.

40 Paediatric subjects with pathological processes (such as benign or malignant tumors, vascular malformations, and Chiari 1 malformations) in the posterior fossa or in the supra-tentorial region, underwent elective or urgent craniotomy/craniectomy. Patients with spontaneous cerebrospinal fluid (CSF) leakage or leakage after Valsalva maneuver following primary dural suture closure were treated either with one or two Evicel-layers ("Evicel") or with additional suture repair ("Sutures").

Intraoperative treatment success (watertight closure) was achieved in overall 23 of 25 (92%) Evicel-subjects, and in 5 of 15 (33%) Sutures-subjects. Further, in posterior-fossa location success was demonstrated in 2 of 4 (50%) Evicel-subjects, and in 0 of 3 (0%) sutures-subjects. Overall efficacy results, based on a meaningful study-design, are considered to be convincing.

Overall, the study documents safe and effective use of Evicel in the paediatric population. Controlled design and clearly favourable efficacy and safety results support an indication for suture support in dura mater closure ("neurosurgery") in children.

☒ Fulfilled:

The procedure is considered to be fulfilled.

The MAH considers that no changes of the product information is needed.

This is not supported as from a legal point of view an adaptation of the SmPC to include the results of the study BIOS-13-006 is mandatory and necessary.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

None.

Clinical studies

Product Name: Evicel Active substance: Human Fibrinogen/Human Thrombin

Study title	Study number	Date of completion	Date of submission of final study report
A Prospective, Randomized, Controlled Study Evaluating EVICEL® Fibrin Sealant as an Adjunct to Hemostasis During Abdominal, Retroperitoneal, Pelvic or Thoracic (Non-Cardiac) Surgery in Pediatric Patients	400-12-006	17 May 2019	15 November 2019
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	BIOS-13-006	17 September 2021	15 March 2022