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Single-arm, open-label, multicentre first in human study to evaluate the safety and performance of dural sealant patch in reducing CSF leakage following elective cranial surgery: the ENCASE trial

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ABSTRACT

Objective The dural sealant patch (DSP) is designed for watertight dural closure after cranial surgery. The goal of this study is to assess, for the first time, safety and performance of the DSP as a means of reducing cerebrospinal fluid (CSF) leakage in patients undergoing elective cranial intradural surgery with a dural closure procedure.

Design First in human, open-label, single-arm, multicentre study with 360-day (12 months) follow-up.

Setting Three large tertiary reference neurosurgical centres, two in the Netherlands and one in Switzerland.

Participants Forty patients undergoing elective cranial neurosurgical procedures, stratified into 34 supratentorial and six infratentorial trepanations.

Intervention Each patient received one DSP after cranial surgery and closure of the dura mater with sutures.

Outcome measures Primary composite endpoint was occurrence of one of the following events: postoperative percutaneous CSF leakage, intraoperative leakage at 20 cm H_2O positive end-expiratory pressure or postoperative wound infection. Overall success was defined as achieving the primary endpoint in no more than two patients. Secondary endpoints were device-related serious adverse events or adverse events (AEs), pseudomeningocele and thickness of dura+DSP. Additional endpoints were reoperation in 30 days and user satisfaction.

Results No patients met the primary endpoint. No device-related (serious) AEs were observed. There were two incidences of self-limiting pseudomeningocele as confirmed on MRI. Thickness of dura and DSP were (mean±SD) 3.5 mm±2.0 at day 7 and 2.1 mm±1.2 at day 90. No patients were reoperated within 30 days. Users reported a satisfactory design and intuitive application.

Conclusions DSP, later officially named Liqoseal, is a safe and potentially efficacious device for reducing CSF leakage after intracranial surgery, with favourable clinical handling characteristics. A randomised controlled trial is needed to assess Liqoseal efficacy against the best current practice for reducing postoperative CSF leakage.

Trial registration number NCT03566602.

Strengths and limitations of this study

- The trial studies a device to prevent postoperative cerebrospinal fluid leakage, which is one of the most common neurosurgical complications.
- The study protocol was performed in multiple centres, registered, prepublished and strictly followed.
- The composite endpoint of the trial reduced the number of inclusions needed.
- The study did not involve a comparison to current clinical standard and has a potential selection bias, so generalisation of results with regard to DSP efficacy needs to be cautiously undertaken.

INTRODUCTION

Cerebrospinal fluid (CSF) leakage is one of the most common neurosurgical complications, occurring approximately in 8% of surgical cases with a higher incidence in complicated skull base surgery, intradural spine surgery and surgery of the posterior fossa.[1–3] Most patients with CSF leakage require a prolonged hospital stay, antibiotic treatment for meningitis, external lumbar drainage, reoperation or a combination of these measures. CSF leakage leads to significant patient burden and expense, with an estimated cost of US$10 000–15 000 per patient per leakage.[2] The use of a dural sealant as an adjunct to primary dural closure is often assumed to further prevent CSF leakage. However, initial approval for liquid sealant

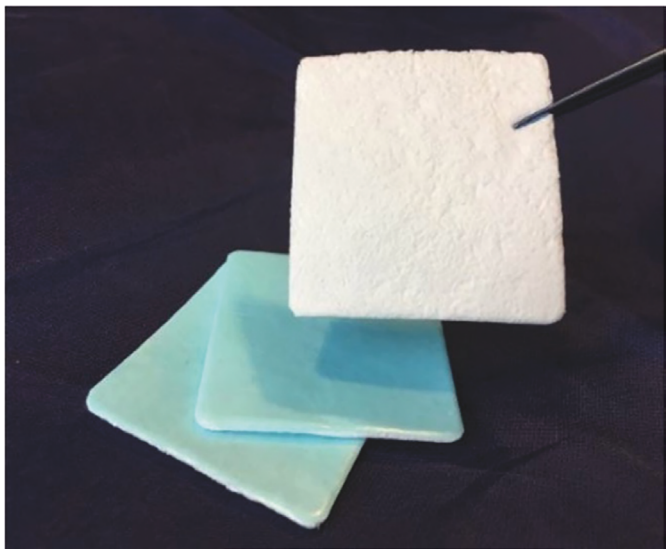

Figure 1 Dural sealant patch/Liqoseal. Produced by Polyganics BV, Groningen, the Netherlands.

was based only on successful intraoperative performance, rates of CSF leakage and other clinically relevant postoperative outcomes, which were similar compared with controls.[3–5]

The sponsor of this study (Polyganics BV, Groningen, the Netherlands) has developed, in close cooperation with our research group, a dural sealant patch (DSP) (figure 1). This bioresorbable patch is intended for use as an adjunct to standard methods of dural closure, such as suturing, to provide a watertight closure of the dura mater to prevent CSF leakage after dural closure procedure. It supports immediate watertight bonding to dura without a liquid component or spray.

Preclinical studies showed better adherence to dura and higher burst pressures than currently used sealants. Biological safety hazards of DSP have been addressed according to International Organization for Standardization (ISO) guideline 10993 (biological evaluation of medical devices)[6] in a series of in vitro and/or in vivo studies: cytotoxicity; sensitisation; irritation; acute, subacute and subchronic toxicity; pyrogenicity; hemocompatibility; genotoxicity; neurotoxicity; local effects; and in vivo degradation up to 12 months. A large implant study in a porcine model showed no arachnoidal adherence or reaction of the brain when directly in contact with the brain (submitted). Based on these data, DSP was considered safe for implantation.

Until the current study, DSP was not tested in human subjects yet. This study aims to study clinical safety and performance of the DSP in reducing CSF leakage in patients undergoing elective cranial intradural surgery with dural closure.

METHODS

This study was conducted as an open-label, single-arm, multicentre study. The study was performed in accordance with the Medical Device Directive (93/42/EEC and Meical Devices Document (MEDDEV) 2.7/3 rev. 3, 2015,[7] MEDDEV 2.7/4,[8] World Medical Association Declaration of Helsinki[9] and ISO 14155:2011.[10] The ENCASE protocol (supplementary material: Clinical Investigational Plan ENCASE) was approved by the Medical Ethical Commission in Utrecht, the Netherlands (NL64477.041.18), the Dutch Inspection for Healthcare and Youth (IGJ) and the Swiss Medical Ethical Board (BASEC 2018–01073). The protocol has been previously published open access in detail[11] (online supplemental appendix 1). The study coordinator and investigators followed accredited Good Clinical Practice (GCP) training, and the study was performed according to GCP regulations. We used the 'Reporting Guidelines Checklist for IDEAL Stage 4' in writing our manuscript.[12]

Public involvement

Patients or the public were not involved in the design, conduct or reporting of our research. The study results were disseminated to study participants via email.

Setting

Three large, tertiary reference neurosurgical centres, two in the Netherlands and one in Switzerland.

Patients

Forty adult patients scheduled for elective cranial surgery with a dural opening of minimal 2 cm were enrolled for this study. At the three individual study centres, patients were screened for participation. Patients needing an intradural drain, electrodes or other devices passing the dura mater after surgery were excluded. All patients gave written consent. Alternatives were discussed, and patients were specifically informed that this was the first clinical application of this device. We stratified into 34 supratentorial and six infratentorial trepanations. First enrolment was on 11 October 2018, last enrolment on 30 April 2019 and last follow-up on 29 April 2020. Detailed inclusion criteria have been published previously.[11] Baseline characteristics are listed in table 1.

DSP

DSP (figure 1) is a flexible patch and consists of two layers: the adhesive layer (white) and the sealing layer (blue). The blue layer consists of biodegradable polyesterurethane (PU). The white adhesive layer is foam-shaped and consists of bioresorbable copolyester. The white foam covalently bonds to the dura due to the incorporated N-hydroxylsuccinimide functionalized polyethylene glycol (PEG-NHS) adhesive component and buffer salt. This layer reacts with amines in the dural tissue in a moist environment, forming covalent bonds between the device and the tissue.

Procedure

Minimally two surgeons per centre participated in the trial; all were individually trained on the protocol. Before dura mature closure, the positive end-expiratory pressure

Table 1 Baseline

	Total (n=40)
Age, mean (SD)	51 (12)
BMI, mean (SD)	26 (4)
Woman	24 (60)
Current smoker	13 (33)
Diabetes	4 (10)
Indication	
Tumour	16 (40)
Functional	13 (33)
Vascular	11 (28)
Craniotomy location	
Supratentorial	34 (85)
Infratentorial	6 (15)
Centres	
A	24 (60)
B	7 (18)
C	9 (23)

Data are presented as numbers (%), unless stated otherwise.
BMI, body mass index in kg/m².;

(PEEP) was increased to 20 cm H_2O for 20 s to check for haemostasis video 1. The dura mater was then closed by suturing with the intention for watertight closure. However, a maximal dural gap of 3 mm was accepted (figure 2A). A substitute (autologous tissue only) could be used by the discretion of the surgeon (figure 2C). The PEEP was increased for the second time to 20 cm H_2O for 20 s to verify saline or CSF leakage out of the dural closure (figure 2E). Each patient then received one DSP after closure of the dura mater. The patch had to overlap the dural opening for at least 5 mm and was slightly compressed with a moist gauze for 2 min (figure 2B, D and F). Exactly 2 min after finishing compression, the PEEP was increased to 20 cm H_2O for 20 s for the third time. The surgeon assessed CSF leakage during and after this PEEP increase until skin closure. All procedures were filmed (video 1) and stored on file.

Video 1 Intraoperative steps of the ENCASE trial

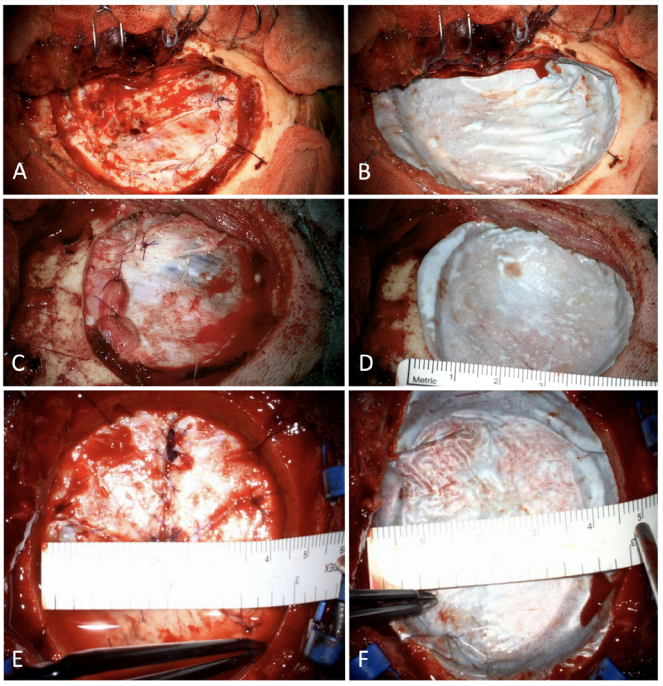

Figure 2 Three patients before and after application of dural sealant patch (DSP). (A) and (B) Patient 6; (C) and (D) patient 14, a piece of muscle as dural substitute is used; and (E) and (F) patient 30, the saline leak is seen basal at 20 cm H_2O before DSP application.

Follow-up

Follow-up of the subjects was performed clinically at day 7 (or at discharge, whichever came first) and at 30, 90 and 360 days after implantation. Additionally, subjects underwent an MRI on day 7 or discharge (whichever came first) and on day 90. All imaging was evaluated and scored by an independent neuroradiologist. The study was controlled and monitored by a clinical research organisation (CRO), Genae (Antwerpen, Belgium).

Endpoints

Primary endpoints

Primary composite endpoint was defined as the occurrence of one of the following events:

- Incidence of wound infection within 30 days as defined in accordance with Centers for Disease Control and Prevention guidelines for superficial incisional, deep incisional and organ space infections (*safety endpoint*).
- Incidence of intraoperative CSF leakage after patch application at 20 cm H_2O of PEEP (*efficacy endpoint*).
- Incidence of percutaneous CSF leak confirmed by β-2 transferrin test up to 30 days after surgery (*efficacy endpoint*).

Secondary endpoints

- Incidence of device-related serious adverse event (SAEs) and adverse events (AEs) throughout the study up to 360 days after surgery. (*safety endpoint*).
- Incidence of wound infections up to 90 days after surgery (*safety and efficacy endpoint*).

- Incidence of percutaneous CSF leak up to 90 days after surgery (*efficacy endpoint*).
- Incidence of pseudomeningocele with the need of puncture, external lumbar drainage or surgical evacuation as assessed by treating physician up to 90 days after surgery.
- Incidence of pseudomeningocele >20 cc as confirmed on MRI (*efficacy endpoint*).
- Thickness dura mater and DSP (combined) in millimetre analysed with MRI (*safety endpoint*).

Additional endpoints

- Incidence of complication requiring a reintervention up to 30 days after surgery. (*safety endpoint*).
- Ease of use and application of the DSP (closed-end questionnaire) (online supplemental appendix 2).

Statistics

The primary (composite) endpoint was scored 'yes' if any of the primary outcome events occurred and 'no' otherwise. This binary outcome was assumed to follow a binomial distribution. Overall study success was defined as the proportion meeting the primary endpoint in 7% or less in the study population, based on previously reported complication rates.[1 2 4 13] Therefore, the number of patients experiencing the primary outcome measure would have to be no more than two for study success. The sample size calculation was based on using a CI approach for one proportion (exact Clopper-Pearson). Based on an expected proportion of 7% on scoring 'yes' on the primary composite endpoint and a target width of 0.20, a 95% CI of 0.012 to 0.209 is obtained with a sample size of 35. Allowing for 12.5% dropout, we aimed to recruit 40 patients for this study.

Data and safety monitoring

Details on data management and safety were published before.[11] Monitoring was provided by a professional independent CRO (Genae, Antwerp, Belgium). The monitor verified all critical data points against the source documents and issued electronic queries for the authorised clinical site personnel to respond. A critical quality control was performed for the first two subjects at each site. A full quality control was performed on the monitored data throughout the clinical investigation, and queries were issued where needed. This process was repeated until the end of the clinical investigation so as to allow for a timeline freezing of the database for statistical analysis.

An independent Data Safety Monitoring Board (DSMB) was installed, consisting of three neurosurgeons not participating in the study with no competing interests, assisted by an independent statistician (online supplemental appendix 3: DSMB charter). The DSMB reviewed all data relating to safety and performance and had a final say on study continuation, thereby ensuring the safety, scientific validity and merit of the study. DSMB analysis was performed after five patients accomplished 30-day follow-up and after 10 patients accomplished 30-day follow-up, at study enrolment completion, at 90-day follow-up completion and at 360-day follow-up completion. At the end of the study, all investigators had access to the final dataset.

Table 2 Outcome

	Total*
Primary composite endpoint†	0 (0; 0–8.8)
Postoperative percutaneous CSF leak (90-day FU)	0 (0; 0–8.8)
Wound infection (90-day FU)	0 (0; 0–8.8)
Intraoperative CSF leakage‡	0 (0; 0–8.8)
Device-related SAEs	0 (0; 0–8.8)
Device-related AEs	0 (0; 0–8.8)
Pseudomeningocele	
Treated§	0 (0; 0–8.8)
>20 cc	2 (5; 1–16,9)
Thickness dura mater and DSP (mm)	
Day 7, mean (SD)	3.5 (2.0)
Day 90, mean (SD)	2.1 (1.2)
User satisfaction 'good' or 'excellent'	40 (100; 91.2–100)

*Data are presented as 'number (percentage of total of 40 patients; 95% CI based on the exact Clopper-Pearson method)' unless stated otherwise.
†Composite of three primary outcome measures; intraoperative CSF leak at 20 cm H_2O positive end-expiratory pressure (PEEP) for 20 s or wound infection within 30 days or postoperative percutaneous CSF leak.
‡Measured at 20 PEEP for 20 s.
§Treated with puncture, lumbar drainage or reoperation.
AEs, adverse events; CSF, cerebrospinal fluid; DSP, dural sealant patch; FU, follow-up; SAEs, serious adverse events.

RESULTS

We screened 46 patients and included 40 patients; four patients failed screening criteria, and two patients withdrew before application. Of the 40 included patients, 24 patients were women. Thirty-four patients received a supratentorial DSP application and six patients an infratentorial DSP application (table 1).

Primary endpoints

No patient reached a primary safety or efficacy endpoint, and therefore, the primary composite endpoint was not reached in any patient (table 2).

Secondary endpoints

During the 360-day follow-up, 214 total AEs were reported. Of these, 18 AEs were reported to be SAEs in six subjects (online supplemental appendix 4). None of the AEs were judged 'definitive device related' by the study coordinator nor by the DSMB. One of the SAEs was marked with 'possibly device related'. This subject was diagnosed with a chemical meningitis, after craniotomy for craniopharyngioma. The direct relation with the study device seems

questionable; however, a potential relationship could not be ruled out. The other recorded (serious) AEs were not related to the device.

No wound infection or percutaneous CSF leak was diagnosed during 90 days of follow-up.

Two subjects reached the secondary efficacy endpoint of a pseudomeningocele of >20 cc confirmed by MRI. These were both self-limiting and proved to be resorbed at 90 days by MRI. These pseudomeningoceles had no clinical consequences for the patients.

Thickness measurements showed no clinically significant swelling of the DSP. Compared with the device thickness before application (~5 mm), the mean thickness after application did not exceed this specified thickness. At day 7, a mean thickness of 3.5 mm (SD 2.0) was measured, and at 3 months, a thickness of 2.1 mm (SD 1.2). In 65% of the subjects, the device was still separately visible on MRI at day 7, which decreased to 20% by day 90.

Additional endpoints

No patient underwent a reoperation within 30 days after surgery.

After every procedure, the neurosurgeon who applied the device answered 'good 'or 'excellent' on the question 'how intuitive was the application of the device?'. Detailed user experience is stated in online supplemental appendix 2.

DSMB evaluation

The final evaluation performed by the DSMB up to day 360 after the last implantation resulted in a recommendation to terminate the trial without any safety concerns. Based on the interim results of the current study combined with all preclinical date CE certification was granted to the DSP on 7 January 2020, which was renamed 'Liqoseal'.

DISCUSSION

With this first clinical study of the DSP (Polyganics BV, Groningen), we demonstrate its general safety and potential efficacy in elective cranial surgery, with none of the patients reaching a primary safety or efficacy endpoint.

The strengths of the current study are a prepublished protocol, a strict adherence to study procedures by training a selective group of surgeons, the involvement of a CRO and its multicentre organisation. Thereby, the use of a composite endpoint reduced sample size.

However, the current study has also some weaknesses. First, a randomised controlled trial (RCT) investigating the safety and efficacy might have provided more robust data regarding the success of DSP. The current trial was primarily a safety trial with a minimal number of patients using a composite endpoint and using a reference rate of published complications to show an effect. We chose this design because a direct RCT was regarded as an unacceptable ethical and financial risk.

A second potential weakness of this study is that one of the primary outcome measures (incidence of intraoperative CSF leakage) was assessed by the operating surgeon, which could have theoretically introduced misclassification of patients and therefore have positively influenced the primary outcome. To prevent this, all procedures had to be filmed and saved in the study database.

Finally, the current study harbours a selective patient population, because we tried to make the ENCASE study population as uniform as possible. Since biocompatibility of autologous tissue is uniform and well described,[14] only this was allowed as a substitute. However, therefore, the interaction with other artificial substitutes remains unknown. Trauma, endoscopic surgeries and spinal surgeries with dural opening were also excluded, while these indications are associated with a higher CSF leakage risk. The added value of DSP in the excluded indications is potentially large but still has to be evaluated more in detail.

Closing the supratentorial dura with or without sealant and its role in CSF leak prevention are the subject of an ongoing debate. Kinaci *et al*[5] performed a meta-analysis of 2321 intradural cranial cases showing no significant difference in CSF leakage rate between the use of a dural sealant (8.2%) and primary closure only (8.4%). Significant difference was found regarding surgical site infection, which was less seen in cases with sealants (RR 0.25, CI 0.13 to 0.48). Osbun *et al*[10] performed a large RCT comparing dural sealing with a PEG hydrogel with 'standard of care'. The absence of CSF leakage at intraoperative Valsalva manoeuvre was used as an inclusion criterium, not as a result variable. In total, 30% was infratentorial and 70% supratentorial, comparable with the current study. Unplanned reintervention rate was 4.2% (study group) versus 4.3% (control), surgical wound complications 3.3% versus 4.3% and postoperative CSF leak 0.8% versus 1.7%. Hutter *et al*[1] performed an RCT comparing standard dural closure using suturing alone with the addition of TachoSil on top. In total, 19% of the procedures were infratentorial and 81% supratentorial. The authors regarded >20 cc pseudomeningocele an indication for treatment, which was also defined as CSF leakage. The difference in leakage rate was not significant with 9.7% in the TachoSil and 17.2% in the control group. Wound infection was 0.9% versus 4.3%. Although these studies are not fully comparable with the current study, we seem to show beneficial results in the current study with neither CSF leakage nor infections and 5% pseudomeningocele >20 cc (which were self-limiting).

Based on the current study, the DSP was CE certified and renamed 'Liqoseal'. To rigorously assess Liqoseal efficacy against the best current practice for reducing postoperative CSF leakage, we have designed a subsequent RCT (ENCASE II, registered on ClinicalTrials.gov under NCT04086550). In this trial, only posterior fossa patients will be included, which are at higher risk for postoperative CSF leak than supratentorial patients. Clinically meaningful outcomes will be compared between Liqoseal and

current standard practice. This study is named ENCASE II and is planned to start recruitment Q2 2021.

In conclusion, DSP/Liqoseal is a safe and potentially efficacious device for reducing CSF leakage after intracranial surgery with favourable clinical handling characteristics.

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Contributors TVD designed the study with Esther Maas-Soer (on behalf of the sponsor) and JWD. TVD, MRG, MS, BB and JF included and operated the patients. TVD, MRG, MS, BB, JWD, JF, PD acquired data assisted by Berber Zweedijk, Paula van Limpt and Elisabeth Jehli. TVD, MRG, and CRO (Genae, Antwerp, Belgium) analysed the data. CRO checked the data and provided statistical advice with MRG. TVD wrote the paper assisted by MRG, BB and AC. MS, BB, AC, JWD, JF, PD, PR and LPR corrected the manuscript versions. All authors approved the manuscript version for publication.

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Competing interests First author received a consultancy fee in the design phase of the product from Polyganics BV, the Netherlands. None of the authors have any other financial interest in the product or Polyganics BV in general.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open-access repository. Extra data can be accessed via the Dryad data repository at https://datadryad.org/stash/dataset/doi:10.5061/dryad.4j0zpc8br.

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POLYGANICS
TRANSFORMING PATIENT RECOVERY

Clinical Investigational Plan

Single-arm, open-label, multicenter study to **e**valuate the safety and performa**nc**e of Dur**a** Sealant Patch in reducing C**S**F leakag**e** following elective cranial surgery

ENCASE

Investigational Device	Dura Sealant Patch
Sponsor	Polyganics BV Rozenburglaan 15A 9727 DL Groningen The Netherlands Tel: +31 50 588 65 88 Fax: +31 50 588 65 99
Manufacturer	Polyganics BV Rozenburglaan 15A 9727 DL Groningen The Netherlands Tel: +31 50 588 65 88 Fax: +31 50 588 65 99
Contract Research Organization (CRO)	genae Group Justitiestraat 6 B 2018 Antwerp Belgium Tel: +32 3 290 03 06
Coordinating Investigator	T.P.C. van Doormaal, MD, PhD UMC Utrecht Heidelberglaan 100 3584 CX Utrecht The Netherlands
Principal Investigators	An updated list of principal investigators, investigation sites and institutions involved will be maintained separately and is available upon request.
Protocol Number	CIP-1
Protocol Version and Date	Version 4; 28 December 2018

POLYGANICS
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Revision History

Version	Update	Reason
4	Section 5 & 6.2.6, 6.2.8	Adaptation of PEEP level elevation. Update of assessment to perform MRI.
3	Flowchart (1.1), Eligibility criteria (6.4) and 7.2.1, 15.	Extension of FU period to 12 months (360 days). And textual changes.
2	Section 6.4, 1 pre-operative exclusion criteria added. Section 11.1 additional information added.	Exclusion criteria added to avoid contra-indications to a MRI. Notification of study to Competent Authority added.
1	Initial Version	Not applicable

POLYGANICS
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Signature Page

Study number *CIP-1*

Study Title *Single-arm, open-label, multicenter study to evaluate the safety and performance of Dura Sealant Patch in reducing CSF leakage following elective cranial surgery [ENCASE]*

Manager QA/RA, Polyganics

Betty IJmker *Digital approval in Q-Pulse**

Manager R&D, Polyganics

Bart-Jan Korteling *Digital approval in Q-Pulse**

Project Manager, Polyganics

Alba Piteira Banga *Digital approval in Q-Pulse**

Clinical Research Manager, Polyganics

Ester Maas-Soer *Digital approval in Q-Pulse**

* *Q-Pulse is an electronic quality management system at Polyganics*

Investigator approval

The Investigator has approved the protocol version [version 4, dated 28 December 2018], and confirms hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the International Standard ISO 14155:2011 and the local legally applicable requirements.

Coordinating Investigator

T.P.C. van Doormaal

POLYGANICS
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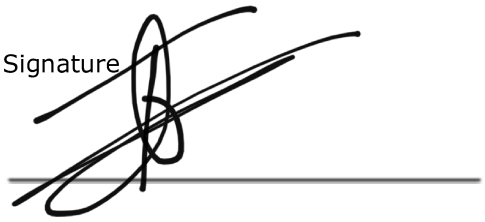
Signature page - Principal Investigator

Principal Investigator at study site*:
I have read and understood this study protocol and agree to conduct the study as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines, the International Standard ISO 14155:2011 and any other applicable local laws and regulations.

Site	*Name and address of site*
Principal Investigator	*Name of PI*

Date 10/17/18

Signature 

**Note: In multicenter studies, this page must be individually signed by all participating Principal Investigators.*

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1. SYNOPSIS

Clinical Investigation Title	**ENCASE** Single-arm, open-label, multicenter study to **E**valuate the safety and performa**NC**e of Dur**A** Sealant Patch in reducing C**S**F leakag**E** following elective cranial surgery
Investigational Device name	Dura Sealant Patch
Primary Objective	The objective of the study is to clinically assess the safety and performance of the Dura Sealant Patch as a means of reducing intra- as well as post-operative CSF leakage in patients undergoing elective cranial intradural surgery with a dural closure procedure.
Clinical Investigation Design	A single-arm, open-label, multicenter study
Clinical Investigation Duration	The total duration of the study is expected to be 16 months (up to 4 months enrolment and 12 months follow-up, see flowchart for visit overview); First enrolment expected in Q3 2018.
Clinical Investigation Population	Subjects undergoing an elective cranial surgery (supra- and infratentorial) with dural closure. The clinical investigation will be conducted on 40 subjects enrolled at up to 3 clinical investigation sites.
Inclusion Criteria	Preoperative 1. Subjects who are able to provide a written informed consent prior to participating in the clinical investigation. 2. Subjects who are ≥ 18 years old. 3. Subjects who are able to comply with the follow-up or other study requirements. 4. Subjects who are planned for an elective intracranial intradural surgery in whom a dural incision of at least 2 cm in length is necessary, which will be closed. 5. Female subjects of child bearing potential must agree to use any form of contraception from the time of signing the informed consent form through 90 days post-surgery. Intraoperative 1. Surgical wound classification Class I/Clean. 2. Minimally 5 mm of dural space surrounding dural opening.

Exclusion Criteria

Preoperative

1. Female subjects who are pregnant or breastfeeding.
2. Subjects with an assumed impaired coagulation due to medication or otherwise.
3. Subjects suspected of an infection requiring antibiotics.
4. Subjects with any type of dural diseases in planned dural closure area.
5. Subjects requiring re-opening of planned surgical area within 90 days after surgery.
6. Subjects requiring local radiotherapy in planned surgical area.
7. Subjects with a known allergy to any of the components (Lactide-Caprolactone co-polyester; Butanediol-BDI co-polyurethane; Polyethylene glycol Succinimidyl Gluterate; Disodium hydrogen phosphate or D&C Green No 6) of the Dura Sealant Patch.
8. Subject who previously participated in this study or any investigational drug or device study within 30 days of screening.
9. Subjects with a presence of hydrocephalus.
10. Subjects with contra-indication to MRI [cardiac pacemaker or defibrillator, severe claustrophobia, injured by a metallic object that was not removed, cochlear (ear) implants, metallic implants (e.g. knee replacement].

Intraoperative

11. Subjects in whom elevation of PEEP or pCO2 has a potential detrimental effect.
12. Subjects who will require a CSF or wound drain, electrodes or other devices passing the dural layer or extra to intracranial bypass surgery.
13. Primary closure of the dura mater with synthetic, non-autologous or autologous material other than galea.
14. A gap > 3 mm after primary closure of the dura mater.

Primary Endpoints

The primary endpoint is a combined endpoint of any neurosurgical events defined as:

<u>Safety</u>

1. Incidence of wound infection confirmed by increase of CRP and positive cultures up to 30 days after surgery;

<u>Performance</u>

2. Incidence of intra-operative CSF leakage after patch application at 20 cmH_2O of Positive End Expiratory Pressure (PEEP);
3. Incidence of percutaneous CSF leak confirmed by β-2 transferrin test up to 30 days after surgery.

Secondary Endpoints

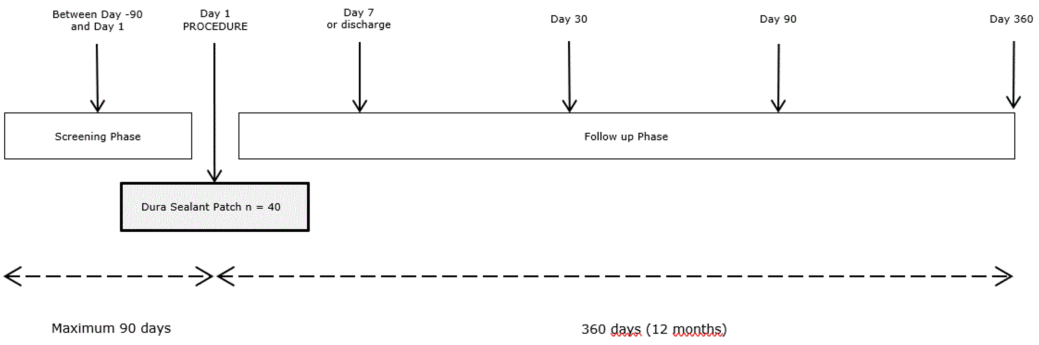
Safety
- Incidence of device related AEs throughout the study up to 90 days after surgery
- Incidence of device related AEs throughout the study up to 360 days after surgery
- Incidence of wound infection confirmed by increase of CRP and positive cultures up to 90 days after surgery

Performance
- Incidence of percutaneous CSF leak confirmed by β-2 transferrin test up to 90 days after surgery
- Incidence of pseudomeningocele with the need of puncture, external lumbar drainage or surgical evacuation as assessed by treating physician up to 90 days after surgery
- Incidence of pseudomeningocele >20 cc as confirmed on MRI
- Thickness dura mater and Dura Sealant Patch (combined) in mm analyzed with MRI

Additional endpoints

- Incidence of complication requiring a re-intervention up to 30 days after surgery
- Ease of use and application of the Dura Sealant Patch

Study schema



1.1 Flowchart of assessments

	SCREENING	**PROCEDURE**	**FOLLOW-UP**			
	Day -90 to Day 1	Day 1	Day 7 or Discharge [a] *(± 1 day)*	Day 30 [b] *(± 5 days)*	Day 90 [b] *(± 14 days)*	Day 360 [b] / EOS *(± 30 days)*
Informed consent	X					
Demographics	X					
Comorbidity, Medical / Surgical History	X					
Eligibility check	X	X				
Physical Exam (inclusive Neurologic exam)	X		X	X	X	
Pregnancy test (female subjects only) [c]	X					
Surgery		X				
PEEP and pCO_2 [d]		X				
Device application		X				
Photo of surgical site [e]		X				
MRI			X	X [f]	X	
β-2 transferrin test [g]			X	X	X	
Inspection wound / clinical signs of infection [h]		Continuously monitored during hospitalization		X	X	
Blood samples [i]			X [i]	X [i]	X [i]	
Phone call						X
Adverse Events		X	X	X	X	X
Medication	X	X	X	X	X	X
User Experience and Device Deficiency		X				

a) Day 7 (± 1 day) or discharge (whichever comes first).
b) Follow-up based on day of Procedure (Day 1).
c) For female childbearing potential subjects only, a pregnancy test will be performed within 48 hours before procedure (urine or blood test).
d) If no spontaneous leakage after sutured closure of dura, PEEP and pCO2 elevation will be performed until CSF leakage occurs. Also after application of the device, this elevation will be performed.
e) Photo to be taken, after sutured closure of dura, pre- and post-application of the device.
f) Only if clinical signs of leakage are present or suspicion of a pocket of fluid by manual palpation, MRI will be performed (applicable at Day 30).
g) Only if external wound leakage is visible or a pocket puncture will be done is, β-2 transferrin test will be performed.
h) During hospitalization, inspection of wound will be monitored continuously as well as signs of infection. Data will be collected from 24 hours after surgery, thereafter every 24 hours until Day 7 or discharge (whichever comes first). Also on Day 30 and Day 90 this data will be collected.
i) Blood samples will be taken for CRP and leucocytes only in case of clinical signs of infection.

2. ABBREVIATIONS AND DEFINITIONS

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse device Effect
CA	Competent Authority
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
e-CRF	Electronic Case Report Form
EC	Ethics Committee
EOS	End of Study
ICF	Informed Consent Form
MDR	Medical Device Regulation
MRI	Magnetic Resonance Imaging
PEEP	Positive End - Expiratory Pressure
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

Surgical wound classification [1]

Class I / Clean	Class I/Clean: An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow nonpenetrating (blunt) trauma should be included in this category if they meet the criteria.
Class II / Clean-Contaminated	An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.
Class III / Contaminated	Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered are included in this category.
Class IV / Dirty-Infected	Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

Intra-operative CSF leakage
CSF leakage after closure of the dura before placement of the bone flap while an elevated CSF pressure is induced.

Post-operative CSF leakage
- percutaneous CSF leakage; leakage of CSF through the wound from the moment the wound is surgically fully closed until 90 days post-operative, and
- pseudomeningocele; accumulation of CSF under the skin from the moment the wound is surgically fully closed until 90 days post-operative.

3. INTRODUCTION

3.1 Background and rationale

The dura mater is the dense, leathery membrane covering and protecting the brain and spinal cord. The dura is a collagenous connective tissue consisting of numerous collagen fibres, fibroblasts, and few elastic fibres arranged in a parallel form. Opening of the dura can be caused by several reasons. It occurs in 30% of neurosurgical procedures, both intracranial as spinal. Also, accidentally during some spinal procedures, where after surgery this defect needs to be closed. Finally, trauma capitis or spinal trauma may damage the dura mater.

The dura is marginally perfused with blood. During surgery, the temporary dry environment and the heat of the operation microscope cause the dura to shrink. This makes stitching the dura to close it often difficult which leads to suboptimal postoperative regeneration of the defect or even absence of regeneration. Especially in the elderly, dura can be paper thin and impossible to handle without damage. Dura behaves totally different than other, better-perfused tissue, like muscle or fascia. In case the dura is not closed watertight this can potentially cause complications. First, the Cerebrospinal Fluid (CSF) can accumulate under the skin (pseudomeningocele) which can hamper proper wound healing and cause complaints like pain. Secondly, it can leak outside through the wound (CSF leakage). This makes normal wound healing impossible. Both complications often lead to an extra intervention and longer stay of the patient in the hospital.

CSF leakage is one of the most common neurosurgical complications, occurring in 4-32% of surgical cases with a higher incidence in complicated skull base surgery, intradural spine surgery and surgery of the posterior fossa [2,3].
The likelihood of CSF leakage as a surgical complication can also depend on age, indication, location of surgery, and underlying pathology. Most patients with CSF leakage necessitate a prolonged hospital stay, antibiotic treatment for meningitis, external lumbar drainage, reoperation, or a combination of these measures. CSF leakage leads to significant patient burden and expense, with an estimated cost of 10,000–15,000 US dollars per patient per leakage [2].
The use of a dural sealant as an adjunct to primary dural closure is often assumed to have value for preventing CSF leakage; yet, few empirical reports describe such an effect.

In a systematic review on all available data in literature, twenty articles were included; ten of these were comparative studies (sealant versus no sealant) including 3 randomized controlled trials. In the 20 articles, a total of 3682 surgical procedures were reported. The number of CSF leakages in general did not differ between the sealant group (8.2%) and control group (8.4%), RR 0.84 (0.50-1.42), I^2=56%. Exclusion of non-RCT's did not alter the results. Meta-analyses for secondary outcomes showed no difference between number of incisional CSF leakage, RR 0.30 (0.05-1.59), I^2=38% and pseudomeningocele formation, RR 1.50 (0.43-5.17), I^2=0%. Surgical site infection was less seen in the sealant group (1.0%) compared to the control group (5.6%), RR 0.25 (0.13-0.48), I^2=0% [4].

Closure of the dura involves several steps. First, the neurosurgeon tries to primarily close the dura with continuous or interrupted stitches. This is possible in 60-70% of intracranial cases and almost 95% of spinal intradural cases (only not in meningioma surgery where the dura is excised or in operations were surgeons on purpose had to increase the intradural space). Watertight closure of the dura is, without any augmentation, per definition not possible because of the puncture holes of the sutures. However, the dura has to be closed as watertight as possible. No protocols exist when to apply an extra substitute over a primarily closed dura instead of suturing only, this is dependent on personal feeling of the operating surgeon. If primary closure is impossible, an autograft (pericranium or muscle) [6] or allograft, xenograft or synthetic substitutes are sometimes sutured in the defect to reduce openings in the dura which are subsequently closed with a

sealant. Native autologous tissue grafts can perform as good as dural substitutes because they do not provoke severe inflammatory or immunological reactions. Potential drawbacks in using autografts are: difficulty in achieving a watertight closure, formation of scar tissue, insufficiently accessible graft materials to close large dural defects, and potential additional incisions for harvesting the graft.
As alternative to the use of an autograft, a non-autologous (allograft) dural substitute can be used. Various xenografts have been studied for this purpose, including bovine and ovine pericardium, porcine small intestinal submucosa, and processed collagen matrices. However, these non-resorbable xenografts are often associated with adverse effects, such as graft dissolution, encapsulation, foreign body reaction, scarring, and adhesion formation.

If the quality of dural closure is improved, complications associated with CSF leakage, including meningitis, pseudomeningocele, impaired wound healing, and subgaleal fluid collection, could be reduced. CSF leakage leads to increased morbidity, prolongation of hospital stay, surgical revision, and enhanced costs as well as possible surgical revisions [3,5].

In daily practice, in approximately 25-50% of all intradural neurosurgical procedures, any adjunct to dural sealing with or without graft is used to prevent CSF leakage and to allow the dura to heal after surgery. This comes down to, in the Netherlands only, 4000-10.000 procedures per year (estimated).

Polyganics BV (medical technology company, Groningen, The Netherlands) has developed in close cooperation with the Brain Technology Institute (Neurosurgical Research Institute, Utrecht, The Netherlands) the Dura Sealant Patch for watertight dural closure after cranial surgery. Detailed description of the device is captured in section 7.1.

This study will be conducted, first time in humans, to clinically assess the safety and performance of Dura Sealant Patch as a means to reduce CSF leakage after dural closure in patients undergoing cranial surgery.

3.2 Pre-clinical data

The following biological safety hazards have been addressed conform ISO 10993 (Biological evaluation of medical devices) [7] in a series of in-vitro and/or in-vivo studies: Cytotoxicity, Sensitization, Irritation, Acute, Sub-Acute and Sub-Chronic toxicity, Pyrogenicity, Hemocompatibility, Genotoxicity, Neurotoxicity, Local effects (up to 3 months) and In-Vivo Degradation (up to 3 months). The last 3 aspects are part of an ongoing dural implantation study in rabbits. Each of these aspects is furthermore addressed by data (up to 6 months) originating from an ongoing porcine implantation study in which next to the safety also the performance of the Dura Sealant Patch is being assessed. The degradation profile and degradation products have moreover been investigated in an in-vitro degradation study as part of the Chemical Characterization that also included investigating the leachables from the device, and the impact of sterilization (electron beam sterilization) on the device.
By combining the results from the above mentioned studies with the chemical characterization the following aspects have also been addressed and specific testing is considered not necessary: Immunotoxicity, Toxicokinetics, Carcinogenicity, Reproductive, Developmental, Teratogenic and Organ toxicity.
Based on the above mentioned studies the Dura Sealant Patch is considered biologically safe for implantation.
More details can be found regarding the results of the pre-clinical testing with the Dura Sealant Patch in the Dura Sealant Patch Investigator's Brochure [8].

4. OBJECTIVE

The objective of the study is to clinically assess the safety and performance of the Dura Sealant Patch as a means of reducing intra- as well as post-operative CSF leakage in patients undergoing elective cranial intradural surgery with a dural closure procedure.

Intra-operative CSF leakage is defined as:
CSF leakage after closure of the dura before placement of the bone flap while an elevated CSF pressure is induced.

Post-operative CSF leakage is defined as:
- percutaneous CSF leakage; leakage of CSF through the wound from the moment the wound is surgically fully closed until 90 days post-operative, and
- pseudomeningocele; accumulation of CSF under the skin from the moment the wound is surgically fully closed until 90 days post-operative.

5. ENDPOINTS

5.1 Primary Endpoint

The primary endpoint is a combined endpoint of any neurosurgical events defined as:

Safety
1. Incidence of wound infection confirmed by increase of CRP and positive cultures up to 30 days after surgery;

Performance
2. Incidence of intra-operative CSF leakage after patch application at 20 cmH_2O of Positive End Expiratory Pressure (PEEP);
3. Incidence of percutaneous CSF leak confirmed by β-2 transferrin test up to 30 days after surgery.

5.2 Secondary Endpoints

Safety
- Incidence of device related AEs throughout the study up to 90 days after surgery
- Incidence of device related AEs throughout the study up to 360 days after surgery
- Incidence of wound infection confirmed by increase of CRP and positive cultures up to 90 days after surgery

Performance
- Incidence of percutaneous CSF leak confirmed by β-2 transferrin test up to 90 days after surgery
- Incidence of pseudomeningocele with the need of puncture, external lumbar drainage or surgical evacuation as assessed by treating physician up to 90 days after surgery
- Incidence of pseudomeningocele >20 cc as confirmed on MRI
- Thickness dura mater and Dura Sealant Patch (combined) in mm analyzed with MRI

5.3 Additional Endpoints

- Incidence of complication requiring a re-intervention up to 30 days after surgery
- Ease of use and application of the Dura Sealant Patch

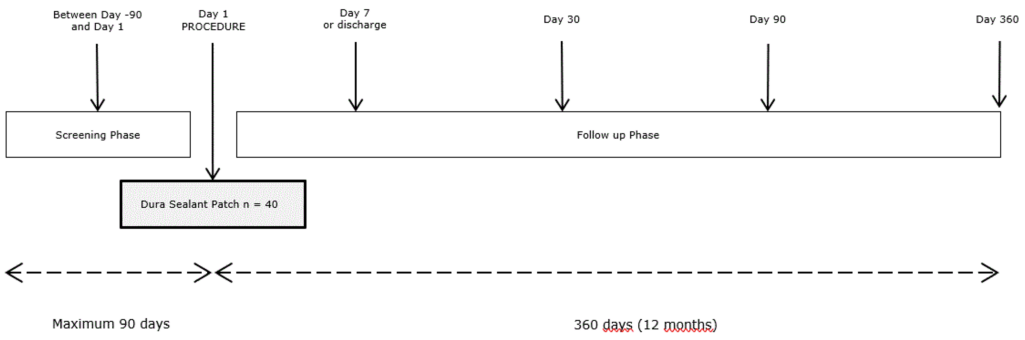
6. DESIGN AND METHODS

6.1 Study design

This study will be conducted, first time in humans, to clinically assess the safety and performance of Dura Sealant Patch as a means to reduce CSF leakage after dural closure in patients undergoing cranial surgery.
The study will be conducted as an open-label, single-arm, multicenter study with a 360 days (12 months) follow up. Up to 40 patients will be enrolled at up to 3 sites in Europe. The list of participating sites will be maintained by Polyganics during the execution of the study, with the final list being part of the Clinical Study Report.

This study has been designed primarily to demonstrate safety and performance of the investigational device to support the design dossier approval in Europe.

In this study, each subject will receive one (1) Dura Sealant Patch after closure of the dura mater. The dura mater will be closed with suturing. If deemed necessary by the surgeon, a substitute (galea only) can be used.
The assessments performed in this study as well as the timepoints are described in the flowchart (see section 1) and the accompanied description in section 6.2.
Based on clinical considerations and literature, a 30 day follow-up is widely regarded as a standard follow up period for most neurological operations. In order to add a safety margin on this standard follow up due to the fact that the product degrades, a follow up period of 360 days is planned. Follow-up of the subjects will be performed at Day 7 (or at discharge whichever comes first) and at 30, 90 and 360 days after cranial surgery.



6.2 Assessments

6.2.1 Informed Consent Form

If a patient decides to participate in this study, one needs to sign the Informed Consent Form (ICF), together with the surgeon (or delegated study team member). One (1) copy is to be kept in the site records. The second (2^{nd}) copy is provided to the patient.

6.2.2 Demographics

Demographic information will be collected at screening to obtain information regarding gender, childbearing potential, age, length, weight and BMI of the patient.

6.2.3 Comorbidity, Medical /Surgical History

At screening, information will be collected about the subjects' medical as well as surgical history (i.e. reason for surgery, allergies, tobacco use, use of medication). Comorbidity will be collected at screening as well.

6.2.4 Physical examination

A physical examination will be performed outlined in the flowchart of assessments (section 1). This examination includes, but not limited to, assessment of the following systems: general, neurologic (neurologic and cognitive deficit check).

6.2.5 Surgery / Device application

Details regarding the surgery and the device will be captured; used size (original or adjusted by cutting) of Dural Sealant Patch, LOT number, location of incision, primary technique for closure of the dura, type & size of suture. The type of suture should be absorbable.

6.2.6 PEEP (Positive End-Expiratory Pressure) and pCO_2

To determine the intra-operative CSF leak before and after the application of the Dura Sealant Patch, the PEEP and pCO_2 (if applicable) will be elevated. This elevation will cause an increase in the intracranial pressure and is to be performed by the anesthesiologist.

The PEEP will be increased until the saline/CSF level rises, with a maximum of 20 cmH_2O. In case the level of saline/CSF has not been raised, in combination with the elevated PEEP, the end-tidal pCO_2 will be increased as well in acceptable steps to a maximum of 6.5%. The achieved level of PEEP, and if applicable the end-tidal pCO_2 level, will be used in the test for the determination of CSF leakage (before and after application of the Dura Sealant Patch).

First, this test will be performed before closure of the dura to determine safety for the postoperative intracranial field (control of hemorrhage, swelling or other potential adverse effects).
Upon completion of the primary sutured dural closure and before application of the device, the closure of the dura will be evaluated for intra-operative CSF leakage with a baseline PEEP (if applicable also the end-tidal pCO_2), unless there is already an obvious spontaneous CSF leak.
After the application of the Dura Sealant Patch and before closure of the cranium, the PEEP (and if applicable the pCO_2) elevation will be repeated to evaluate for intra-operative CSF leakage.

6.2.7 Photo of surgical site

A photograph will be taken before and after the device application. This photograph will need to include the subject ID as well as a ruler. The ruler will need to have a metric system with at least a mm-scale. The photographs need to be uploaded into the e-CRF.

6.2.8 MRI assessment

Magnetic Resonance Imaging (MRI) is a non-invasive imaging technology that produces three dimensional detailed anatomical images without the use of radiation. In the study MRI imaging will be performed to diagnose, if any type of leakage is present.
All subjects will undergo an MRI on Day 7 or discharge (whichever comes first). On Day 30, a MRI will only be performed, if clinical signs of leakage are present, or suspicion of a pocket of fluid by manual palpation. Additionally, on Day 90, a MRI will be performed unless not already scheduled. A Day 90 MRI will be performed to collect data on the long-term thickness of dura mater and investigational device.
This diagnostic assessment will collect amount of fluid available above and below the dura. An independent radiologist will analyze the MRIs of all subjects for the outcome measurements.

6.2.9 β-2 transferrin test

β-2 transferrin is a form of the protein transferrin that is present in CSF, but not usually found in blood, nasal secretions or other body fluids. It can be used as an endogenous marker of CSF leakage.
Only if external leakage from wound is visible, minimally 2-3 drops of fluid will be collected in a sterile container/vail to perform a β-2 transferrin test. If clinical indication requires a pocket puncture, the β-2 transferrin test will also be performed.
Sample collection and analysis will be done according to standard procedures at the site.

6.2.10 Clinical signs of infection / Wound inspection

During the hospitalization, the subject will be daily monitored for clinical signs of infection. The surgical wound will be inspected daily starting 24 hours after surgery. Data will be collected from 24 hours after surgery thereafter every 24 hours until Day 7 or discharge (whichever comes first). For the study, the clinical data listed below will be collected as outlined in the flowchart of assessments (section 1). If deemed necessary by the investigator, additional data on different timepoints can be collected.
The clinical data to be collected in the e-CRF includes the following:

- Body temperature.

In case of signs of infection the following data will be collected as well:

- C-Reactive Protein (CRP) test
- Leucocytes
- Culture of wound.

6.2.11 Laboratory tests

The tests listed below will be performed as outlined in the flowchart of assessments (section 1). In addition, laboratory tests may be performed at various unscheduled time points, if deemed necessary by the investigator. Sample collection and analysis will be done according to standard procedures at the site.
The laboratory tests include the following:

- Pregnancy test (test will be performed for women with childbearing potential only within 48 hours before procedure (urine or blood serum test)
- CRP in case signs of infection
- Leucocytes in case of infection

6.2.12 Adverse Events

Adverse Events will be documented directly after application of the investigational device till the last follow up contact (or EOS visit). During this period, (serious) adverse events and (serious) anticipated and unexpected adverse device effects will be recorded. See section 10.1 for the definition of Adverse Events.

6.2.13 Medication

At screening, an overview of medication use will be documented. Throughout the rest of the study, medication with emphasis on anticoagulants, antibiotics, corticosteroids and anti-epileptic drugs will be documented.

6.2.14 User experience

After the procedure, surgeons are invited to complete several closed-end questions regarding their user experience with Dura Sealant Patch. Questions include application of the device. Also the legibility of labels and opening of the package is included.

6.3 Patient population

The study is planned to enroll up to 40 subjects, scheduled for elective cranial surgery (supra- and infratentorial), up to 3 clinical investigation sites. In practice, the proportion of patients based on the location of surgery (supra- versus infratentorial) is around 7:1. This estimate is based on the amount of surgeries (including both elective and trauma procedures) at 2 of the participating sites in recent history.
The aim in this study will be to enroll according to a ratio of 7:1 (supratentorial : infratentorial) in order to address the complete indication area. A maximum of 25 subjects will be enrolled per site.
The patient population will be recruited by the associated neurosurgeons at the clinical investigational sites.

6.4 Indication and selection criteria

6.4.1 Preoperative inclusion criteria

Subjects will be eligible according the following criteria:

1. Subjects who are able to provide a written informed consent prior to participating in the clinical investigation.
2. Subjects who are ≥ 18 years old.
3. Subjects who are able to comply with the follow-up or other study requirements.
4. Subjects who are planned for an elective intracranial intradural surgery in whom a dural incision of at least 2 cm in length is necessary, which will be closed.
5. Female subjects of child bearing potential must agree to use any form of contraception from the time of signing the informed consent form through 90 days post-surgery.

6.4.2 Preoperative exclusion criteria

Subjects who meet any of the following criteria will be excluded from participation:

1. Female subjects who are pregnant or breastfeeding.
2. Subjects with an assumed impaired coagulation due to medication or otherwise.
3. Subjects suspected of an infection requiring antibiotics.
4. Subjects with any type of dural diseases in planned dural closure area.
5. Subjects requiring re-opening of planned surgical area within 90 days after surgery.

6. Subjects requiring local radiotherapy in planned surgical area.
7. Subjects with a known allergy to any of the components (Lactide-Caprolactone co-polyester; Butanediol-BDI co-polyurethane; Polyethylene glycol Succinimidyl Gluterate; Disodium hydrogen phosphate or D&C Green No 6) of the Dura Sealant Patch.
8. Subject who previously participated in this study or any investigational drug or device study within 30 days of screening.
9. Subjects with a presence of hydrocephalus.
10. Subjects with contra-indication to MRI [cardiac pacemaker or defibrillator, severe claustrophobia, injured by a metallic object that was not removed, cochlear (ear) implants, metallic implants (e.g. knee replacement].

During the intracranial surgery, the patients also need to comply with the intraoperative criteria.

6.4.3 Intraoperative inclusion criteria

Subjects will be eligible according the following criteria:
1. Surgical wound classification Class I/Clean.
2. Minimally 5 mm of dural space surrounding dural opening.

6.4.4 Intraoperative exclusion criteria

1. Subjects in whom elevation of PEEP or pCO2 has a potential detrimental effect.
2. Subjects who will require a CSF or wound drain, electrodes or other devices passing the dural layer or extra to intracranial bypass surgery.
3. Primary closure of the dura mater with synthetic, non-autologous or autologous material other than galea.
4. A gap > 3 mm after primary closure of the dura mater.

6.5 Point of enrolment

Patients are considered enrolled in the clinical investigation when they have signed the ICF, meet all inclusion criteria, meet none of the exclusion criteria and the Dura Sealant Patch has contacted the patient's dura. No patients will undergo study specific screening procedures before signing the ICF.

6.6 Patient numbering

Patients are assigned a study identification number after signing the ICF. This number is not related to any personal data as it is pseudonymized. The number will consist of 5 digits; a combination of site and enrolment number. For example, 01-001; for which the site is captured as the first 2 digits and the last 3 digits for enrolment number at the site.

6.7 Screen failures

Subjects who are eligible based on the pre-operative criteria and signed ICF will be further screened intra-operative. If then it is noted the subject is ineligible based on the intra-operative criteria, subject is considered a screen failure. The reason for screening failure will be recorded in the electronic case report form (e-CRF).

6.8 Early withdrawal of patients

6.8.1 Early withdrawal criteria

A patient can withdraw consent or stop participation at any given time during the study. Patients will not be obliged to provide a reason for their withdrawal. There will be no penalty for withdrawal. Withdrawal will not have any consequences for the medical treatment of the patient. Further treatment will occur following standard practice.

Data of withdrawn patients collected up until the point of withdrawal, will be preserved and used in the analyses of the study results, unless the patients specifically indicates that the data should not be used. The reason for discontinuation must be recorded in the source documentation and the e-CRF. Possible reasons for discontinuation of participation may include, but are not limited to, the following reasons:

- Subject decides to withdraw from the study;
- Adverse Events;
- Lost to follow-up: after three unsuccessful attempts to reach the patient by telephone, a registered mail will be sent to the patient to indicate the need for a follow-up appointment. If these communications are unsuccessful, the patient will be considered lost to follow-up.

6.8.2 Treatment failures

Incorrect application (removal of the Dura Sealant Patch after placement, replacement or lateral translation) is considered treatment failure. When the application of Dura Sealant Patch fails, the patient will receive the most optimal method for dura closure as regarded by the surgeon. The patient will then receive common follow-up care and will not need to complete the scheduled study follow-up. The end of the procedure (surgery) will be the EOS for the patient.

7. INVESTIGATIONAL DEVICE

7.1 Investigational device

7.1.1 Intended use

The bioresorbable Dura Sealant Patch is indicated for use as an adjunct to standard methods of dural closure, such as suturing, to provide a watertight closure of the dura mater to prevent CSF leakage after dural closure procedure.

7.1.2 Investigational device description

The Dura Sealant Patch is a flexible patch which consists of two layers: the adhesive layer and the sealing layer (see Figure 1).

One side of the patch consists of a white layer (foam-shaped, consisting of bioresorbable co-polyester); the adhesive layer. The white foam needs to be placed on the dura mater and will strongly adhere to the dural tissue due to the incorporated adhesive component and buffer salt.
This foam layer, with the incorporated PEG-NHS adhesive, reacts with amines in the dural tissue in a moist environment, forming covalent bonds between the device and the tissue. The other side of the product, the passive sealing layer is a sheet made from blue colored bioresorbable polyurethane (PU). This layer forms the watertight seal, intended to prevent CSF leakage. The colorant is added to clearly distinguish between the sides of the product, so the correct side [white layer] will be placed to the dura.

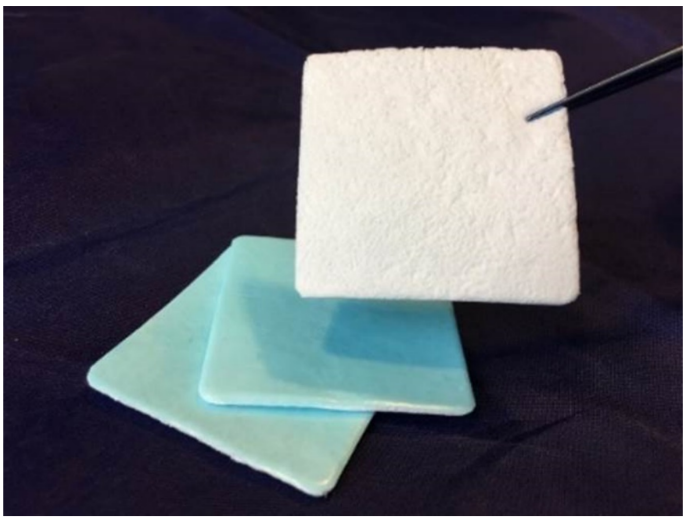


Figure 1 Polyganics Dura Sealant Patch investigational device with an adhesive white foam layer and passive blue sealing layer

7.1.3 Investigational device sizes

Catalogue #	Length [cm]	Width [cm]	Weight [mg]
DS01-024/08	8	8	1600-2000

7.1.4 Device identification

All investigational devices will have a batch/LOT number with the following sequence: DURYYYYMMDDXX, where DUR stands for Dura Sealant Patch, YYYY MM DD for the date of manufacturing and XX for the sequence of the lot number.

7.2 Surgical procedure for using the device

The following instructions for placement of the Dura Sealant Patch are mandatory to achieve watertight closure with the Dura Sealant Patch:

Pre-operative

1. Take the package with the Dura Sealant Patch out of the freezer at least **10 minutes** and maximum of 8 hours, before use.
2. Immediately remove the outer box and keep the pouch closed. Pouch and blister are **not sterile**.

Intra-operative

1. Dura mater should be closed with standard method of suturing.
2. Rinse the dura mater surface from particles (such as bone dust) with physiological saline.
3. Dura mater surface should be moist (remove excessive fluid if applicable).
4. In case of bleeding, this should be stopped.
5. Open the aluminum pouch and also the inner blister (both not sterile).
6. **DO NOT press the Dura Sealant Patch before application (white foam layer should not be compressed manually since it will not expand after being compressed).**
7. If the size of the trepanation is smaller than the Dura Sealant Patch, cut into the required size.

8. Cutting should be done by using a dry and sterile instrument (e.g. scissors) with the white side facing up.
9. Place the **white side** of the dry Dura Sealant Patch against the sutured area of the dura mater, without pre-moistening the patch.
    a. Place on the suture (or dura substitute; galea only) with a gap of maximum 3 mm or smaller.
    b. Cover at least 5 mm beyond the margins of the gaps in the sutured area at all edges.
10. To position the Dura Sealant Patch correctly, compress the Dura Sealant Patch with the fingers; compression of the foam fixates the patch and is necessary for adhesion.
11. For an equal pressure distribution;
    a. Use a moist gauze (gauze should not be dripping) and cover the complete Dura Sealant Patch with this gauze.
    b. Hold down the Dura Sealant Patch with a gentle pressure; equal to approximately one (1) kilogram, for a minimum of two (2) minutes.
12. Remove the light pressure and gauze carefully after at least two (2) minutes. There is no residual product which needs to be removed since the entire Dura Sealant Patch will fully resorb.

7.2.1 Explantation of device

The Dura Sealant Patch is a degradable device and not meant to be explanted. The only reason for explanation is when an adverse event occurs, and it is necessary to remove the device. As the device will degrade, it may be that no complete device will be present.

In case an unexpected re-operation has to be performed within 2 weeks after primary surgery, it is likely the device can be totally explanted if deemed necessary by the surgeon. This hypothesis is based on preclinical studies (porcine study and subsequent histological analysis). It is expected that after the 2 week timepoint total removal of the patch will be increasingly difficult due to ingrowth of autologous fibrotic tissue in the device. It is also expected that the device will degrade *in vivo* in 6-12 months and thereby slowly transform into a new fibrotic layer (the so called 'neodura'). Since there will probably be no significant adherence to the brain, it is expected that in those particular cases the surgeon will be able to open the patch/neodura as normal dura.
Normally, if re-surgery is needed after 3-6 months, dura can be adherent to the brain independent of the sealant. In that case local/individual standard techniques by the neurosurgeon will be applied.
In case explantation of the Dura Sealant Patch is required, a picture has to be taken before and after explantation, and an analysis of the removed tissue will be performed on discretion and assignment of the surgeon at the site. The procedures followed will be based on the reason for explantation. On request, the information of the analysis will be provided to the Sponsor.

7.3 Training of users

The device users will be neurosurgeons who are trained in dural closure during cranial surgery.
All users in the clinical investigation will be trained on the device and correct use by the sponsor (or delegate) during the site initiation visit.
A presentation will be given by the sponsor (or delegate) including the following:

- Device: composition, function, mode of action, form and size
- Device indications, precautions, warnings and possible adverse effects
- Pre-, Intra- and Post-operative procedures
- Device handling and suturing

At the end of the training, the surgeon will acknowledge and sign off on the training record. A product specialist from the sponsor (or delegate) will also attend the first (1st) surgery to observe and facilitate the procedure.

7.4 Total number of devices intended for clinical investigation

Only one (1) device will be applied per study subject. In agreement with the site, the sponsor will provide a sufficient amount of devices at the beginning of the study. New investigational devices will be supplied to the site based on the amount used until the end of the enrolment period.

7.5 Receipt, storage, dispense and return of the Dura Sealant Patch

The investigator is responsible for device accountability at the site. This responsibility can be delegated to an appropriate staff member.
The investigational devices will be provided to the sites directly from the sponsor, arranged by the Polyganics' Clinical department in collaboration with Polyganics' shipment department.
Together with the devices, the site will also receive a Device Accountability Record Form on which receipt, usage and return (if applicable) will need to be recorded.

The investigator should document on the Device Accountability Record Form the receipt of investigational devices at the site, the inventory at the site, administration to each subject and the return of devices to Polyganics BV. This includes dates, quantities, lot numbers, expiry dates and subject identification numbers.
All devices must be stored and used according to storage requirements indicated in the device labelling and the Instructions For Use.
In case of device malfunctions or product complaints, the device should be kept at the site until Polyganics BV provides instructions for return of the device for analysis. The investigator should inform Polyganics BV within 24 hours after discovery of the device malfunction or product complaint. Return of devices should be noted on the Device Accountability Record Form including date, quantity, lot number, expiry date and reason for return.

8. STATISTICAL ANALYSIS

8.1 Introduction

As described in section 6, the study will be conducted, first in humans, as an open-label, single-arm study with the primary endpoint as defined in section 5. This study will be conducted to evaluate the safety and performance of the Dura Sealant Patch.

8.2 Sample size calculation

For the purpose of sample size calculation, the primary outcome measurement is assumed to be the composite of the three primary endpoints. Each patient will score 'yes' if any of the three occurs, and 'no' otherwise. This binary outcome is assumed to follow a binomial distribution.

The percentage of patients scoring 'yes', along with an exact (Clopper-Pearson) two-sided 95% confidence interval for percentage, will be reported. Overall study success will be concluded if the percentage of patients scoring 'yes' is 7% or less.
This is based on a previously reported neurological complications rate of 7.7% (Osbun ea) [9].

As this is a single group pilot study, the sample size calculation is based on specifying the width of the confidence interval around the primary outcome measure, rather than aiming to demonstrate non-inferiority or superiority to a given complication rate.

If the percentage observed in the study were to be 7%, 35 patients would be required for a confidence interval with width no more than 20%. For study success, as defined above, the number of patients experiencing any of the three complications, would have to be no more than 2 in this case.
Allowing for 12.5% dropping out, the study will aim to recruit 40 patients.

The diagram below summarizes the results of the sample size calculation and required patient numbers, allowing a drop-out rate of 12.5%.

Reported percentage in the study	Width of 2 sided 95% CI (Clopper-Pearson)	Sample size	Sample size (including 12,5% drop-out)
7%	20%	35	40

8.3 Outcome analysis

All individual data will be listed. Adherence to the protocol (e.g. in/exclusion criteria, times of measurement, completeness and consistency of data, etc.) will be checked using the data recorded. Standard statistical parameters (number of non-missing values, mean, median, standard deviation, maximum and minimum) or frequency tables will be calculated where appropriate. Baseline characteristics will be tabulated and differences will be examined and described.

Analyses will be based upon enrolled patients: all patients who meet the eligibility criteria, signed the Patient Informed Consent Form and have been surgically treated with the Dura Sealant Patch will be included in the analyses.

8.4 Incomplete / missing data

It is not intended to estimate any missing data, which cannot be obtained from the investigator by interpolation or any other methods.

9. RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

A risk analysis according to the ISO 14971:2012 - Application of risk management to medical devices [10], has been conducted. Risks will be minimized or eliminated through appropriate design control, confirmed by pre-clinical bench, laboratory and animal testing.

9.1 Anticipated clinical benefits

In the current treatment of closure of dural opening after cranial surgery, there is no defined standard of care within neurosurgery. Both sealants as well as suturing only are treatments used. The added values of these different treatments are often assumed, but rarely well described in the literature. This is also reflected in no defined standard of care.

The investigational device adheres to the dura mater and provides a watertight closure bridging small gaps. This adhesion avoids posterior CSF leakage. Complications associated with CSF leakage, including meningitis, pseudomeningocele and impaired wound healing could be reduced.
The clinical benefit may be the reduction of the accompanied complications with CSF leakage. Another benefit may be the ease of use of the device as it can be applied directly out of the package without extra actions regarding preparation.

9.2 Anticipated adverse device effects

During the preclinical testing in animals (pigs), there were 2 observations in regards to a possible relation to the device, but had no clinical consequences to the animals. See also Investigators Brochure [8].
Adverse device effects in humans could occur, which are not yet known.

9.3 Residual risks associated with the investigational device

Even though this is a novel medical device with regards to safety and use in the intended area, there is minor risk for extremely rare or unknown side effects developing from the treatment.
The individual components of the device are well known and used in other marketed products. The specific combination of components for the intended use of this product has been extensively tested through in vivo, in vitro and chemical testing.
However, there is still a residual risk that the barrier function of the device might not be sufficient to reduce occurrence or recurrence of CSF leakage. This residual risk will be mainly covered by lot release of the device, to ensure proper adhesion to the dura mater; as well as various validations such as packaging and sterilization, to ensure no loss of adhesion properties overtime.

9.4 Risks associated with participation in clinical investigation

The risks of the surgical procedure include post-operative complications, as well as any potential complications during the surgery which is performed under anesthesia. The risks include but are not limited to, infection, inflammation, discomfort at the surgical site, and neurological complications resulting from the procedure (none device related).
In terms of application of the device, the potential risks are mainly associated to untrained personnel, which will be covered by a device training to be completed by all participating surgeons and general personnel, clear labelling and by the provided IFU, before start of the study.

9.5 Possible interactions with concomitant medical treatment

Interactions with concomitant medications in humans are not known. However, in the *in-vivo* studies no interactions were reported.

9.6 Risk mitigation

Extensive safety testing on the product according to ISO 10993 and ISO 14971 was conducted to minimize and mitigate the risks to subjects and users. Pre-clinical studies demonstrate the device performs as intended and meets the performance specifications including biological testing. This biological testing demonstrated that the product is biologically safe for implementation in humans and can be used as intended.
The clinical protocol incorporates several procedures to minimize the risks to subjects and to ensure the benefits of the clinical study outweigh its potential risks. These include:

- Subjects in the study will undergo frequent visits and routine medical follow-up to help detect any abnormal changes and to provide appropriate treatment if necessary.
- The study will be monitored to ensure the identification, documentation and analysis of adverse events; and to ensure compliance with the protocol and procedures that are in place for conducting research to protect the safety and well-being of all subjects.
- Surgeons will be experienced with dural closure methods and will receive training form the sponsor on device specific protocol.

9.7 Risk-to-benefit rationale

Based on preclinical studies, as well as the current known risks of dural closure methods, the risk to benefit ratio for using the Dura Sealant Patch is within reason for foreseeable risks. However, preclinical studies do not always predict the side effects humans may experience. Additionally, complications due to individual subject response to an implanted device may necessitate future dural closure procedures. Close observation and follow-up of patients is required as outlined in the protocol.
As previously mentioned, training procedures, lot release testing and various validations will minimize the risks to patients and ensure the benefits of the clinical use outweigh its potential risks. Since there is a low risk for safety issues related to the use of the device and the risk of CSF leakage can be reduced with this device post-operatively, the general safety risks associated with a surgical intervention are outweighed by the benefit of absence of post-operative CSF leakage.

10. SAFETY REPORTING

During the study, (serious) adverse events and (serious) anticipated and unexpected adverse device effects will be recorded [11]; reporting will be done from point of enrolment. Safety of the subjects participating in this clinical investigation will be monitored throughout the clinical investigation using the Adverse Event reporting process in the EDC system, to identify real and potential safety issues.
Adverse events will be reported according to the ISO 14155:2011 [11], while recognizing and following the requirements including reporting timelines specified in other specific laws, regulations, directives, standards and/or guidelines as appropriate and as required by the countries in which the study is conducted.
Any serious adverse events, investigational medical device deficiency, and new finding/updates in relation to already reported events will be reported in accordance to the MEDDEV 2.7/3 [12] to all National Competent Authorities where the clinical investigation has commenced.

10.1 Definition of Adverse Events

10.1.1 Adverse Device Effect (ADE)

An AE related to the use of an investigational medical device.
Note 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, operation, or any malfunction of the investigational medical device.
Note 2: This definition includes any event resulting from the use error or intentional misuse of the investigational medical device.

10.1.2 Adverse Events (AE)

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.
Note 1: This definition includes events related to the investigational medical device or the comparator.
Note 2: This definition includes events related to the procedures involved.
Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

AE's will be documented directly after surgery till the last follow up contact.

10.1.3 Serious Adverse Events (SAE)

A Serious Adverse Event (SAE) is an adverse event that:
a) led to a death,
b) led to a serious deterioration in the health of the subject user or other persons that either resulted in:
   1) a life-threatening illness or injury, or
   2) a permanent impairment of a body structure or a body function, or
   3) in-patient or prolonged hospitalization, or
   4) medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
c) led to foetal distress, foetal death or a congenital abnormality or birth defect

Note: A planned hospitalization for pre-existing condition or a procedure without a serious deterioration in health is not considered to be a SAE.

10.1.4 Unanticipated Adverse Device Effect (UADE)

An Unanticipated Adverse Device Effect (UADE) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

10.1.5 Serious Adverse Device Effect (SADE)

An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

10.1.6 Anticipated Serious Adverse Device Effect (ASADE)

An adverse device effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

10.1.7 Unanticipated Serious Adverse Device Effect (USADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

10.1.8 Device Deficiency (DD)

The inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.
Note: Device deficiencies include malfunctions, use errors, and inadequate labelling.
Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence

a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate,

shall be reported under the same conditions as a SAE.

10.1.9 Malfunction

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or Clinical Investigation Plan.

10.2 Safety Reporting Process – (principal) investigator responsibilities

The (principal) investigators shall report all adverse events and device deficiencies in the appropriate sections of the e-CRF and provide where requested by the sponsor, the necessary clinical or technical information that may contribute to clarifying the circumstances.
The (principal) investigators shall report all serious adverse events (SAEs) and device deficiencies (DDs) that might have led to a SAE: if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate, and new findings/updates in relation to already reported events to the sponsor and record in the e-CRF within 24 hours after awareness of the event.
Any other reportable events as described above or a new finding/update to a reported event shall be reported immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.
The principal investigator shall document all adverse events and device deficiencies in the e-CRF from the point of enrolment until the subject is exited from the study.

10.3 Emergency Contact Details for reporting SAEs and SADEs

In case of emergency, contact the CRO and the Sponsor by e-mail, phone or fax:

At the CRO

genae associates NV

Email address encase@genae.com
Fax number +32 (0)3 290 03 07

At the Sponsor

Polyganics BV

Ester Maas-Soer (Clinical Research Manager)
Email address e.maas-soer@polyganics.com
Phone number +31 (0)50 588 65 88

10.4 Information provided by the clinical investigation site

The principal investigator will provide the following information, at a minimum, for each adverse event (AE) or Adverse Device Effect (ADE):

- Date of the AE or ADE.
- Date Principal Investigator (or authorized designee) became aware of AE or ADE
- Description of AE or ADE, relevant diagnostic findings
- Treatment
- Resolution
- Assessment of:
  1. severity of the event
     a. Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
     b. Moderate: minimal, local or noninvasive intervention indicated; limiting
     c. Severe: medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling
        i. Life-threatening: urgent intervention indicated, disabling
        ii. Fatal: death related to AE
  2. relationship of the event to the investigational device (yes, no, possibly)
  3. relationship of the event to the index procedure (yes, no, possibly)
  4. causality
     a. disease under study
     b. lack of performance of the investigational device or comparator/worsening of treated condition
     c. medical history
     d. concomitant or previous medication
     e. other (specify)

The principal investigator will supply the sponsor and/or designee, with any additional information related to the safety reporting of a particular event upon request.

10.5 Sponsor responsibility

The sponsor is responsible for the classification of all adverse events and ongoing safety evaluation of the clinical investigation and shall:

- Review the investigator's assessment of all adverse events and determine and document in writing their seriousness, severity and relationship to the investigational device; in case of disagreement between the sponsor and the

principal investigator(s), the sponsor shall communicate both opinions to concerned parties.
- Review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties.
- Ensure the reporting to the EC of all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or by the EC.
- Review and report all reportable events (including device deficiencies) according to national regulations in acceptable timely conditions and shall monitor for increased incidence and severity.
- Report all relevant safety information to the Data Safety Monitoring Board (DSMB) in a timely manner, per the DSMB Charter.
- Ensure that the EC or other applicable regulatory authorities are informed of significant new information about the clinical investigation, and
- In case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, determine whether corrective or preventive action is required.

10.6 Data Safety Monitoring Board

A Data Monitoring Committee (DMC), also called a Data Safety Monitoring Board (DSMB), is a group of individuals with pertinent expertise that, on a regular basis, reviews accumulating data from an ongoing clinical study. The DSMB advises the sponsor regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the study.
In this study, the DSMB will be established to review data relating to safety and performance and to ensure the continued scientific validity and merit of the study, according to the DSMB Charter to be established for this protocol. Further details regarding the timing and content of the interim reviews (for the purpose of monitoring study conduct and assessing patient safety) is included in the DSMB Charter.

11. ETHICS AND REGULATORY CONSIDERATIONS

The study will be performed in accordance with the Medical Device Directive (MDD 93/42/EEC and MEDDEV 2.7/3 rev. 3; 2015) [12], MEDDEV 2.7/4 [13], World Medical association Declaration of Helsinki (Appendix A) and ISO 14155:2011 [11]. Local and national laws/regulations concerning clinical investigations will be observed as well as any requirements as posed by the CA's/EC's overseeing the study.

11.1 Ethics Committee and Competent Authority

The CIP will be submitted to the appropriate Ethics Committee (EC). Written approval form the EC must be obtained prior to enrolling any patients, and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed and the date of approval.
Modifications made to the CIP after receipt of the EC approval must also be submitted as amendments to the EC in accordance to local procedures and regulations.
The EC will receive annual written reports on the progress of the investigation if required. Written notification of completion, termination or discontinuation of a site should be provided to the EC.
On local requirements, the Competent Authority (CA) will be notified according to local laws. For the Netherlands, the study will be send to IGJ after approval of the Dutch EC.
The applicable EC(s) and CA(s) will be also be notified of the reported SAE's.

11.2 Informed Consent

Prior to signing the Informed Consent Form (ICF), patient information should be given in a language and fashion understandable to the patient. Information should be provided written as well as oral. Patients should not be coerced, persuaded or unduly influenced to (continue to) participate in the study. Patients should be given ample time (at least 24 hours) and opportunity to enquire information regarding the study, ask questions regarding their possible treatment and enrolment and to consider their participation. All questions should be answered to the satisfaction of the patient.

Patient informed consent must be obtained prior to any study activities. The ICF should be signed and dated by the patient, and the person conducting the informed consent discussion. In case the patient is unable to read and understand the ICF, a witness should be present during the entire informed consent discussion. This witness should also sign the ICF, stating that informed consent was freely given by the patient. The patient has to receive one of the two (2) signed and dated copies of the ICF.

The ICF should be updated or amended whenever new information becomes available that may be relevant to the patient. The ICF should be approved by the required EC.

11.3 Subject compensation in case of injury

Covering the duration of the clinical investigation, a No-Fault Clinical Investigation Insurance is in place, to enable compensation in the event of an injury to a participating subject.

11.4 Confidentiality

All information to be sent to Polyganics BV concerning patients and their participation in the study will be considered confidential. All data will be used in a manner without identifiable reference to the individual patient.

12. MONITORING

The monitor will contact and visit the investigator regularly and will be allowed, on request, to have access to all source documents needed to verify the entries on the e-CRF and other protocol- related documents; provided that subject confidentiality is maintained in agreement with local regulations. It will be the monitor's responsibility to inspect the e-CRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered. Sponsor monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs and the recording of the main safety and performance endpoints. Additional checks of the consistency of the source data with the e-CRFs are performed according to the study-specific monitoring plan.

The investigator must ensure that subjects' anonymity will be maintained. On e-CRFs or other documents submitted to the sponsor, subjects should not be identified by their names, but by the subject number. The investigator must keep a subject identification code list showing the enrolment number, the subject's name, date of birth and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., subjects' signed informed consent forms) should not be sent to the sponsor and must be kept by the investigator in strict confidence.
The investigator and co-investigators agree to cooperate with the monitor(s) to ensure that any issue detected in the course of these monitoring visits are resolved. If the subject is hospitalized or dies in a hospital other than the study site, the investigator is in charge of contacting this hospital in order to document this SAE.

The investigator shall supply the sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

An initiation visit will be performed before the first subject is included. Monitoring visits and contacts will occur at regular intervals thereafter, according to a frequency defined in the study-specific monitoring plan. A close out visit will be performed after study closure.

13. DATA HANDLING AND RECORD KEEPING

Research coordinators at the clinical site will perform primary data collection drawn from source document (hospital records) reviews. The e-CRF will be completed on a continuous basis starting from the point of enrolling the subject to final follow up. The sponsor or designee will provide clinical monitoring, including review of e-CRF with verification to the source documentation. This may include worksheets retained with the e-CRF documentation and hospital records.

13.1 Database Management and Quality Control

Data will be collected through an EDC (electronic data capturing) system on the e-CRF, a secure, internet-based case report form and image transfer software. This system will be used to record all subject information collected in the clinical investigation for secure data tracking and centralized data monitoring ("remote monitoring").
Automated, real time data analyses built into the database enable complete control on study outcomes and safety assessments. Automated alerts (emails) are generated by the system for enrolment of subjects, serious adverse event notification, and upcoming or late follow up visits. Additional specific alerts and reports may be setup as required by the sponsor to ensure full control and easier compliance to the clinical investigation plan.

The principal investigator or his/her designee at the clinical site will perform primary data collection by entering the data into the e-CRF, using a standard internet-browser. Only the principal investigator or other pre-designated clinical investigation site personnel will be authorized to enter data (from source documents) via internet-based e-CRF, using a unique user name and password. Each user access to the system is tracked, so that all data operations can be monitored and verified.

The sponsor's designated monitor shall ensure appropriate training is provided to all site personnel involved prior to the start of the clinical investigation.
The principal investigators, using their personal login information shall approve and date each case report form section in the EDC system.
The principal investigator can delegate tasks to his/her collaborators, however the roles and responsibilities and time period of involvement for each clinical site personnel must be documented on the site personnel log and appropriate training should be received before getting involved with the clinical investigation.
Clinical site personnel not trained and not officially identified by his/her name, signature and personal login for the EDC system cannot access the system nor enter data in the e-CRFs.
The monitor, using his/her personal login information shall verify all critical data points against the source documents and issue electronic queries for the authorized clinical site personnel to respond.
A case report form section shall be considered complete when all data are completed, verified by the monitor, outstanding queries resolved and signed off by the principal investigator.

A critical quality control shall be performed for the first 2 subjects by the sponsor's designated data management team and queries issued where needed. Such queries must be reviewed by the monitor prior to alerting the site personnel to answer them.
After the monitor has done the source document verification and obtained satisfactory answers to eventual queries from the site, a full quality control shall be performed on the monitored data throughout the clinical investigation by the designated data management team and queries issued where needed. This process will be repeated till the end of the clinical investigation so as to allow for a timeline freezing of the data base for statistical analysis.

13.2 Remote monitoring

Remote or centralized monitoring is a remote evaluation carried out by sponsor personnel or representatives (e.g., data management personnel, statisticians, or clinical monitors) at a location other than the site(s) at which the clinical investigation is being conducted. Remote monitoring processes can provide many of the capabilities of on-site monitoring as well as additional capabilities.
In addition to onsite monitoring visits, remote monitoring of the data entered in the e-CRF system will be used to achieve the following:

- Conduct activities such as: standard checks of range, consistency, and completeness of data and checks for unusual distribution of data, such as too little variance).
- Special attention will be given in case of frequent data anomalies or errors, protocol violations or excessive drop outs.
- Augment on-site monitoring by performing monitoring activities that can only be accomplished using centralized processes (e.g., statistical analyses to identify data trends not easily detected by on-site monitoring).
- Monitor data quality through routine review of submitted data in real-time to identify missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic and/or significant errors in data collection and reporting at the site.
- Verify source data remotely, provided that both source data and e-CRFs can be accessed remotely.
- Conduct aggregate statistical analyses of study data to identify subject data that are outliers relative to others and to evaluate individual subject data for plausibility and completeness.
- Conduct analyses of site characteristics, performance metrics (e.g., high screen failure rates, high frequency of eligibility violations, and delays in reporting data), and clinical data to identify early on corrective actions needed for characteristics correlated with poor performance or noncompliance.

14. CLINICAL INVESTIGATION CONDUCT RESPONSIBILITIES

The sponsor of this study, Polyganics BV, is overall responsible for the conduct of the study. This includes assurance that the study is conducted according to the Declaration of Helsinki, ISO 14155 [11], and local and national laws. These responsibilities may be delegated to consultants and/or Contract Research Organizations.

14.1 Duties of the sponsor

Sponsor' duties may be delegated to a CRO. General duties of the sponsor include submitting applications and information to appropriate regulatory authorities as required by local and national regulations, obtaining regulatory approvals before allowing shipment of devices, selecting investigators, ensuring proper clinical site monitoring and ensuring patient informed consent prior to participation.

All records as required by local and national regulations will be maintained by the sponsor. All required reports will be submitted to local and national regulations. Investigators' site files including all records and reports of the study will be retained for at least 15 years after the completion or termination of the study. Discarding may only be upon notice from the sponsor. Investigators should contact the sponsor prior to discarding the records to avoid error.
After completion or termination of the study, a final report should be prepared. This critical evaluation of all data collected in the study at all sites. This report should be read and signed by all investigators and be provided to the required local and national authorities. Any modifications in this report should be reviewed by Polyganics BV before submitting.

14.2 Amendments

No changes in the clinical investigation procedures shall be effected without mutual agreement of the principal investigator and the sponsor. The agreement of the changes must be documented by signing the corresponding clinical investigation plan amendments. All changes require notification to the EC and the CA (when appropriate). Substantial changes may require approval from the EC and the CA prior to implementation.

14.3 Deviations from the clinical investigational plan

A deviation from the clinical investigation plan is defined as an event where the clinical investigator or site personnel did not conduct the study according to the clinical investigation plan, ISO 14155:2011 [11] and any national or local regulatory requirements.

For reporting purposes, the sponsor classifies study deviations as major and minor:
Major deviation: Any deviation that may either have an impact on the rights, safety and well-being of the subjects or the scientific outcome of the clinical investigation.
Minor deviation: Any deviation that has no impact on the rights, safety and well-being of the subject or that may impair the scientific outcome of the clinical investigation.

Deviations, along with explanations of why these occurred, are recorded by the principal investigator in the appropriate section of the e-CRF, and reviewed with the sponsor's designated monitor for the need for reporting to the EC, and any corrective and/or preventative actions to be taken.
Major deviations are to be reported immediately by the principal investigator to the overseeing EC and where required by national regulations to the CA by the sponsor.
Repeated deviations after discussion with the sponsor's designated monitor and after implementation of corrective and preventative actions by the site personnel may lead to a decision from the sponsor to suspend temporarily the clinical investigation in a given site until full corrective actions have been put in place. Failure to do so may lead to termination of the clinical investigation in this site.

14.4 End of clinical investigation

The end of clinical investigation is defined as the last participant's last visit. At any time, the investigators and/or the sponsor have the right to temporarily suspend or terminate the clinical investigation for clinical or administrative reasons.

For example:
- Ethical concerns
- Insufficient subject recruitment
- When safety of subjects is doubtful or at risk
- Early evidence of benefit or harm of the experimental intervention.

Polyganics BV reserves the right to terminate a site for any of the following reasons:
- Repeated failure to complete case report forms

- Failure to obtain informed consent
- Failure to enroll patients
- Failure to report Serious Adverse Events within 24 hours of knowledge
- Loss of investigational inventory
- Repeated protocol violations with lack of taking preventive and/or corrective actions.

Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the EC will be promptly informed about the reason(s) for the termination or suspension.

15. INTELLECTUAL PROPERTIES AND PUBLICATION

1. All information regarding the Dura Sealant Patch, data generated by this study, operations, patent applications, manufacturing processes, and scientific data shall be the exclusive property of Polyganics BV. Investigators are obliged to provide Polyganics BV with all data obtained within the study. This confidential information may be published only in collaboration with the sponsor.
2. Any publication or public presentation of study data, including the manuscript as per 15.4 hereunder, collected in this study should be reviewed in writing by Polyganics BV prior to any publication or presentation. Draft material should be provided to Polyganics BV for review at least 30 days prior to submission or presentation date. Polyganics BV may require that the Investigators delete from their documents any reference to Polyganics BV's confidential information. If Polyganics BV does not provide the Investigators with its feedback within such 30 days period, the Investigators shall be free to publish or present such data.
3. Within one year after the end of the study, the Investigator or Polyganics BV will submit a final study report with the results of the study, including any publications/abstracts of the study, to the local Ethics Committee and the Competent Authority.
4. The trial will be registered at ClinicalTrials.gov. Subject to Polyganics BV's rights as per 15.2 above, a manuscript, which at least describes the study and the answer to the primary research question(s) will be submitted to a major clinical journal within a reasonable time after closure of the database. The aim to close the study database will be within two months after the last scheduled follow-up date of the last patient.

16. REFERENCES

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5. Kim KD et al. Polyethylene glycol hydrogel spinal sealant (DuraSeal Spinal Sealant) as an adjunct to sutured dural repair in the spine: results of a prospective, multicenter, randomized controlled study. Spine (Phila Pa 1976) 2011;36:1906–1912

6. Pettorini BL et al. The use of a reconstituted collagen foil dura mater substitute in paediatric neurosurgical procedures - Experience in 47 patients. British Journal of Neurosurgery 2010;24(1):51–4

7. ISO 10993-1:2009. Biological evaluation of medical devices, www.iso.org

8. Investigator's Brochure, Dura Sealant Patch, Polyganics BV, Final version

9. Osbun JW et al. A multicenter, single-blind, prospective randomized trial to evaluate the safety of a polyethylene glycol hydrogel (Duraseal Dural Sealant System) as a dural sealant in cranial surgery. World Neurosurg. 2012;78(5):498-504

10. ISO 14971:2012. Application of risk management to medical devices, www.iso.org

11. ISO 14155:2011. Clinical investigation of medical devices for human subjects – Good Clinical Practice, www.iso.org

12. MEDDEV 2.7/3 rev.3 (May 2015) Clinical investigations: serious adverse reporting under directives 90/385/EEC and 93/42/EC

13. MEDDEV 2.7/4 (December 2010) Guidelines on clinical investigation: a guide for manufacturers and notified bodies

17. APPENDICES

17.1 Appendix A - Declaration of Helsinki

WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give

informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

User Experience of Surgeon		
Determination which side of the device to place on the dura mater is easy		
Very easy	n (%)	22 (55.0%)
Easy	n (%)	16 (40.0%)
Not easy/ Not hard	n (%)	2 (5.0%)
Hard	n (%)	0 (0%)
Very hard	n (%)	0 (0%)
Missing	n (%)	0 (0%)
How would you judge the preparation time (including thawing)?		
Excellent	n (%)	5 (12.5%)
Good	n (%)	26 (65.0%)
Neutral	n (%)	9 (22.5%)
Poor	n (%)	0 (0%)
Bad	n (%)	0 (0%)
Missing	n (%)	0 (0%)
How would you judge the ability to cut the device?		
Excellent	n (%)	8 (20.0%)
Good	n (%)	32 (80.0%)
Neutral	n (%)	0 (0%)
Poor	n (%)	0 (0%)
Bad	n (%)	0 (0%)
Missing	n (%)	0 (0%)
How would you judge the application of the device onto the tissue without the introduction of wrinkles?		
Excellent	n (%)	0 (0%)
Good	n (%)	27 (67.5%)
Neutral	n (%)	12 (30.0%)
Poor	n (%)	1 (2.5%)
Bad	n (%)	0 (0%)
Missing	n (%)	0 (0%)
How does the device follow the contours of dura during or after application?		
Excellent	n (%)	6 (15.0%)
Good	n (%)	32 (80.0%)
Neutral	n (%)	2 (5.0%)
Poor	n (%)	0 (0%)
Bad	n (%)	0 (0%)
Missing	n (%)	0 (0%)
How intuitive was the application of the device?		
Excellent	n (%)	6 (15.0%)
Good	n (%)	34 (85.0%)
Neutral	n (%)	0 (0%)
Poor	n (%)	0 (0%)
Bad	n (%)	0 (0%)
Missing	n (%)	0 (0%)
How would you judge the procedure to compress the device?[1]		
Excellent	n (%)	1 (2.5%)

Good	n (%)	33 (82.5%)
Neutral	n (%)	6 (15.0%)
Poor	n (%)	0 (0%)
Bad	n (%)	0 (0%)
Missing	n (%)	0 (0%)

Appendix 2 Surgeon user experience.

[1] The 'compression' refers to the 2 minute compression of the device needed after initial application.

heeft verwijderd: 1

DATA SAFETY AND MONITORING BOARD CHARTER			
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Polyganics BV
Rozenburglaan 15A
9727 DL Groningen
The Netherlands

Single-arm, open-label, multicenter study to evaluate the safety and performance of Dura Sealant Patch in reducing CSF leakage following elective cranial surgery

ENCASE

CONFIDENTIAL

Charter

Version: 1.0 **Date:** 21-NOV-2018

Revision history

Version	Date (dd-MON-YYYY)	Changes
1.0	21-NOV-2018	Initial release

Note: This Charter will serve as the Standard Operating Procedure (SOP) for the Data Safety and Monitoring Board (DSMB).

Signature Page

I have read this charter and agree with its content. I will conduct my responsibilities on the DSMB as outlined herein.

W.P. Vandertop, MD
DSMB Chairperson

Date _____ Signature _____

R. Dammers, MD
DSMB Member

Date _____ Signature _____

PWA Willems, MD
DSMB Member

Date _____ Signature _____

Prepared by: Anik Hermans, Sr. Clinical Safety Manager
genae

Date _____ Signature _____

DATA SAFETY AND MONITORING BOARD CHARTER			
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1 ABBREVIATIONS

AE	Adverse Events
CA	Competent Authority
DSMB	Data Safety and Monitoring Board
EC	Ethics Committee
FDA	Food and Drug Administration
SAE	Serious Adverse Events
SOP	Standard Operating Procedure

2 QUALITY ASSURANCE

The following reference documents have been used as the guidance for the composition and operation of the DSMB, as described in this Charter.

Reference	Title
ISO14155	Clinical investigation of medical devices for human subjects – Good clinical practice (Second edition, 2011-02-01)
FDA	Guidance for Clinical Study Sponsors: On the Establishment and Operation of Clinical Study Data Monitoring Committees.
EMEA/CHMP/EWP/5872/03 Corr	Guideline on Data Monitoring Committees
Protocol	ENCASE: Single-arm, open-label, multicenter study to evaluate the safety and performance of Dura Sealant Patch in reducing CSF leakage following elective cranial surgery CIP-1

3 GENERAL

3.1 Introduction

This Charter will outline the roles and responsibilities of the Data Safety and Monitoring Board DSMB established for the ENCASE study sponsored by Polyganics BV (hereafter referred to as Polyganics) and will serve as the Standard Operating Procedure (SOP) for the DSMB.

The charter defines the DSMB, its membership, and the purpose and frequency of its meetings. The charter also provides the procedures for ensuring confidentiality, the guidelines for communication, and an outline of the content of the reports provided to the DSMB.

3.2 Roles and responsibilities

Data Safety and Monitoring Board

The DSMB is responsible for assessing data during the course of a study in a manner that contributes to the scientific and ethical integrity of the study. The DSMB's recommendations will provide the sponsor with an overall scientific, safety, and ethical appreciation of the study, and should assist the sponsor in maintaining the rigor of the study design, with appropriate attention paid to the protection of human subjects.

The DSMB is responsible for determining its operational procedures and acting in accordance with its approved DSMB Charter. If changes to the Charter are required, amendments will be prepared by genae and agreed to by the DSMB.

The DSMB members will:

- Work according to the last approved version of the protocol and the procedures described in this charter;
- Review any protocol amendments, addendums or modifications since previous meeting;
- Define DSMB processes and study stopping guidelines prior to the first data review;
- Periodically review and monitor aggregated and individual subject data related to safety, data integrity, scientific validity and overall conduct of the study, to ensure the rights, safety, and welfare of the study participants;
- Monitor subject accrual and retention;
- Review formal interim safety analysis and evaluate the benefit/risk balance (if applicable);
- Provide in writing recommendations to Polyganics concerning the continuation, modification, or termination of the study;

In addition to the above, the DSMB Chairperson will:

- Serve in a leadership role and conduct DSMB meetings;
- Oversee the overall scientific integrity of data review;
- Review and approve the meeting report.

genae

In addition to operational support, and serving as a liaison between DSMB and Polyganics, genae is responsible for overall coordination of DSMB activities to ensure that the DSMB maintains smooth and efficient operations throughout the study genae will:

- Compile and report (S)AEs to the DSMB, as appropriate;
- Compile and report overviews describing the progress of the study to the DSMB, as appropriate;
- Prepare relevant summary data reports in response to DSMB inquiries (This may include analyses not otherwise outlined in this charter, based upon findings);
- Facilitate the DSMB meetings;
- Maintain documentation and records of all activities;

Polyganics

The sponsor will be responsible for activities including but not limited to:

- Selection and formation of the DSMB;
- Communication with Competent Authorities (CA), Ethics Committees (EC) and investigators, in a manner that maintains integrity of the data, as necessary (This communication is not the responsibility of the DSMB);
- Promptly report potential safety concern(s) to the DSMB;

3.3 Documentation

Throughout the duration of the study, the DSMB will be apprised of all new safety information relevant to the device and the study. This includes providing the DSMB with a copy of the protocol in advance of the first meeting, as well as promptly providing any revisions. All safety reports issued by the sponsor and other pertinent documents relating to the study will be provided.

3.4 Membership

The DSMB consists of at least 3 specialists in the field of neurosurgery, with specialization and relevant clinical expertise documented by a recent signed and dated CV. The names of the DSMB members, their affiliations, and contact information are listed in Attachment 1.

The DSMB members are independent from Polyganics and the participating investigators without any financial, scientific or other conflict of interest in the trial. Written documentation specifying the absence of any conflict of interest will be present prior to the start of the activities and has been collected by the sponsor. The members must immediately report any changes in the conflict of interest/ financial disclosure that occur during the course of the study. Any questions or concerns that arise regarding conflicts of interest will be addressed by the DSMB Chairperson with input from other DSMB members, genae and Polyganics as necessary.

The DSMB members will receive financial compensation for their time and their expenses will be reimbursed. Details regarding financial compensation and payment schedule will be handled on an individual basis with each DSMB member and will not be described in this charter.

Members must have sufficient availability to attend all planned and ad hoc meetings as needed, and must understand the time commitment required for data review for the duration of the trial.

The sponsor will appoint the DSMB Chairperson.

4 DATA REVIEW PROCEDURES

4.1 Meetings

Frequency of meetings

The DSMB meetings will take place according to the following schedule:

- Meeting 1: DSMB kick-off meeting
- Meeting 2: when the first 5 patients accomplish the 30 days follow-up visit
- Meeting 3: to review the interim analysis requested by the Swiss authorities (10 patients accomplish 30 days follow-up visit); during this meeting, and based on the reviewed information, the members will decide on whether a 3rd meeting is necessary, and when.

The first meeting will be a webex meeting in order for the members to:

- Form an understanding of the protocol and the definitions being used;
- Establish a meeting/data review schedule;
- Establish list of events that will trigger the DSMB review;
- Form the study modification and/or termination guidelines;

The DSMB will then meet via teleconference/webex, depending on the need.

An emergency meeting of the DSMB may be called at any time by the Chairperson or any other party involved in the Study, should questions arise related to the patient's safety.

Polyganics and genae Safety Team may seek the DSMB advice for any reason outside of scheduled meetings.

Meeting structure

Meetings may be convened as conference calls, as well as in person.

Meetings must be attended by at least 2 DSMB members. If 2 members provide different opinion, a 3rd member must be consulted.

If the DSMB decides to issue a recommendation to terminate the Study, all DSMB members present must vote for or against the recommendation. Majority vote will rule in the event of a split vote and a statement written by the committee members who did not vote with the majority, outlining their opinion (a minority report), should be appended.

A genae facilitator will attend the DSMB meetings as a non-voting member in order to facilitate data presentation and follow-up reporting.

Each DSMB meeting can consist of an open session and a closed session. The open session may be attended by representatives of Polyganics. Only the DSMB members will have voting rights

Minutes of the open session will be recorded by genae. Minutes will be finalized upon signature of the DSMB Chairperson and maintained by genae in accordance with applicable statutory regulation. A copy of the minutes will be provided to Polyganics.

The closed session will be restricted to the DSMB members. The genae facilitator, who is not the member of the clinical team, may attend the closed session upon DSMB approval. The minutes of the closed session will be recorded by the DSMB Chairperson or genae facilitator, if present. Minutes from the closed session will be recorded separately from the minutes of the open session and stored securely by genae. Closed session minutes, finalized by signature of the DSMB Chairperson, will be maintained in confidence and retained until the end of study, after which the minutes will be provided to Polyganics.

Following each meeting, a formal report, separate from the minutes of the open and closed sessions, describing the DSMB recommendations and rationale will be prepared by genae facilitator and sent to the members of the DSMB within 1 week after the meeting. The report will divulge no detail of DSMB discussions, only the final recommendation (Attachment 3).

Once approved by all members, the report will be sent to the Polyganics.

4.2 Safety updates

During the active[1] phase (up to 1 month follow up) of the study, safety updates will be provided via e-mail to the different members after each patient reaches the 30 days follow-up (1 update per patient).

[1] The active phase is considered as the period of enrollment up to the moment of the follow up related to the primary endpoint of the Study. In case the primary endpoint moment takes place during a long-term follow up (> 6 months

These updates will be sent by e-mail and include data specified in Attachment 2. If requested by the DSMB members, the SAE report and relevant source data (if available) will be provided.

For the remaining duration of the study, monthly updates will be provided during the data collection period.

Additionally, a safety update will be submitted to the DSMB as soon as possible after the 10th patient is enrolled and completed the 30-day follow up visit. This update will include the follow-up results up to 30 days post index procedure and will be reviewed by the DSMB during a meeting (as indicated above).

The DSMB will review the data and provide their feedback via email to genae.

A written statement must be prepared by each DSMB member within 10 calendar days of receipt of the safety update. This statement will involve the following 2 options:

1. No safety concern
2. Safety concern.

In case of a safety concern, a rationale should be given. In case no answer is received from 1 or more of the members and/or no 2 equal responses are received from at least 2 members, an urgent reminder to the members that did not yet responded is sent by genae.
In case the DSMB considers that there might be a safety issue, Polyganics will be informed and a DMSB meeting will be set up as soon as possible.

4.3 Stopping rules

No stopping rules were defined; the members will review the safety updates on a case-by-case basis and will evaluate if the AE incidence rates are comparable to what they see in daily practice; if deemed necessary, stopping rules will be defined afterwards.

4.4 DSMB Communication of Findings and Recommendations

The DSMB may recommend suspension or termination of the study based on the detection of unanticipated safety issues, such as higher event rates than anticipated, composite and/or individual major adverse events, primary endpoints, device failures, or unexpected/unanticipated SAEs and which might indicate there is a safety concern for the subject population, users or others. The DSMB will take into account the incidence and nature of the reported events, the causal/temporal relationship of the events to the device, previous experience with the device, and the known event rate from the literature. In the event of recommendation for suspension or termination, the DSMB Chairperson will promptly notify genae facilitator. genae will arrange a meeting or teleconference with Polyganics, genae, and the DSMB to occur (if possible) within 5 working days.

While DSMB recommendations are not legally binding, they do require professional consideration by the Polyganics.

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after the previous visit), regular updates should be provided on a monthly basis during the moment of the data collection.

4.5 Polyganics Response to DSMB Findings and Recommendations

If the DSMB recommends continuation of the study without modification, no formal response will be required. However, if the recommendations request action, such as a recommendation for termination of the study or modification of the protocol, the DSMB will request that Polyganics provide a formal written response, within 5 working days, stating whether the recommendations will be followed and the plan for addressing the issues.

Upon receipt, the DSMB will consider the response of Polyganics and will attempt to resolve relevant issues, resulting in a final recommendation. Appropriate caution will be necessary during this process to avoid compromising study integrity or the ability of Polyganics to manage the study, should the study continue. Polyganics will agree to disseminate the final decision to the appropriate regulatory agency, EC, and investigators within an appropriate time.

In the unlikely event of irreconcilable differences between the DSMB and Polyganics, especially regarding study termination or other substantial study modifications, the DSMB can, based on ethical considerations, step down as advisory board and express objection to continue monitoring the current study. This decision will be communicated to Polyganics and genae.

Public disclosure of the final decision of Polyganics or DSMB recommendations will be at the discretion of Polyganics. Neither the DSMB nor genae will make any public announcements either as a group or individually.

5 AMENDMENTS TO THE DSMB CHARTER

This DSMB charter can be amended as needed during the course of the study. Information to be included as amendments will be any modifications or supplements to the reports prepared for the DSMB, as well as amendments to other information addressed in this charter. Each revision will be reviewed and agreed upon by Polyganics, genae, and the DSMB. All versions of the charter will be archived in accordance with this document.

6 ARCHIVING OF DSMB ACTIVITIES AND RELATED DOCUMENTS

All DSMB documentation and records will be retained by genae until final study transfer to Polyganics. Access to archived data will be controlled by the genae which will release the information only as specified in this charter or as required by law.

7 CONFIDENTIALITY

All materials, discussions and proceedings of the DSMB are confidential. Members, and other participants in DSMB meetings, are expected to maintain the confidentiality.

ATTACHMENT 1 - CONTACT DETAILS

Data Safety and Monitoring Board

Name and Function:	Prof. Dr. W.P. Vandertop DSMB Chairperson
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Name and Function:	Dr. Ruben Dammers DSMB member
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Name and Function:	Dr. P.W.A. Willems DSMB member
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ATTACHMENT 2 - DSMB WEEKLY/ MONTHLY UPDATES

The following information will be provided to all DSMB members:

Safety

- Overview of the reported event(s)[2] including the following information:
  - Unique subject identifier.
  - Date of event including calculation of days since procedure.
  - Type/description of event.
  - SAE (Yes/No)
  - Relation to the study device
  - Relation to procedure
  - Event action / treatment and outcome.
  - Device deficiencies

Study conduct

- Current enrolment status (only during enrollment phase)
- Protocol deviations
- Subject follow-up status (overview of follow up visits completed to date), if applicable

[2] Tabular overview in PDF and xlsx formt

ATTACHMENT 3 - DSMB MEETING REPORT

To: Polyganics
Meeting date: DD-MON-YYYY
Study: ENCASE
Meeting Attendees: <…>

The DSMB charged with the review of safety data for the ENCASE study reviewed DSMB Data Report dated DD-MON-YYYY

Summary of discussions in open session of the meeting: <…>

As a result, the DSMB recommendation is:

☐ To continue the study unmodified until next scheduled meeting.

☐ To continue the study unmodified, and plan an additional meeting: DD-MON-YYYY (to be confirmed with Sponsor)

☐ To continue the study unmodified, and request additional expert review/analyses.

<Describe and provide timelines of additional review>

☐ To set up a meeting with Polyganics to discuss concerns of safety within the ENCASE study as outlined below.

☐ To suspend the study due to <…>

☐ To terminate the trial for the reasons outlined below.

Additional Comments:

<NAME>
Chairperson, Data Safety Monitoring Board for ENCASE

Signature: Date:

Appendix 4 SAE listing

Patient ID	Start / End date	AE description	SAE? [a]	SAE criteria [b]	Date / cause of death [c]	Serious deterioration in health resulted in:	If hospitalized, date of admission / discharge	Severity	Device related	Procedure related	Action taken	AE outcome	Date of resolution / stabilization
01-006	13NOV2018 / 04FEB2019	Pulmonary Embolism	Yes	Serious deterioration in the health of the subject		Hospitalization (initial or prolonged)	06NOV2018 / 16NOV2018	Mild	Not related	Probable	Medical therapy	Completely recovered/ Resolved	04FEB2019
01-006	13NOV2018 / 21NOV2018	pneumonia	Yes	Serious deterioration in the health of the subject		Hospitalization (initial or prolonged)	06NOV2018 / 16NOV2018	Mild	Not related	Probable	Medical therapy	Completely recovered/ Resolved	21NOV2018
01-006	20MAR2019 / 12NOV2019	Increase dyspnoea, which is caused by multiple components.- pulmonary embolism.-possible cardiac component - restrictive lungfunction due to high standard left diaphragm (iatrogenic)	Yes	Serious deterioration in the health of the subject		Hospitalization (initial or prolonged)	06JUN2019 / 13JUN2019	Moderate	Not related	Unlikely	Medical therapy	Completely recovered/ Resolved	12NOV2019
01-006	08NOV2019 / 13NOV2019	dyspnoea, hypotension, hyperventilation	Yes	Serious deterioration in the health of the subject		Hospitalization (initial or prolonged)	08NOV2019 / 13NOV2019	Moderate	Not related	Not related	Medical therapy	Completely recovered/ Resolved	13NOV2019
01-007	13NOV2018 / 17DEC2018	Dysfasia	Yes	Serious deterioration in the health of the subject		Hospitalization (initial or prolonged)	12NOV2018 / 20NOV2018	Moderate	Not related	Definite	Medical therapy	Completely recovered/ Resolved	17DEC2018

[a] SAE = Serious adverse event

[b] all criteria for serious adverse event that apply

[c] if serious adverse event is death

Patient ID	Start / End date	AE description	SAE? [a]	SAE criteria [b]	Date / cause of death [c]	Serious deterioration in health resulted in:	If hospitalized, date of admission / discharge	Severity	Device related	Procedure related	Action taken	AE outcome	Date of resolution / stabilization
01-014	25JUL2019 / 27JUL2019	Heatstroke, where patient also experiences hyperthermia and was less awake. Which led to a possible hypocortisal crises	Yes	Serious deterioration in the health of the subject		Hospitalization (initial or prolonged), Medical/surgical intervention to prevent life threatening illness or injury or permanent impairment	25JUL2019 / 27JUL2019	Severe	Not related	Probable	Medical therapy	Completely recovered/ Resolved	27JUL2019
01-014	25JUL2019 / 02AUG2019	Renal impairment due to heatstroke, Furosemide use, drank to little.	Yes	Serious deterioration in the health of the subject		Hospitalization (initial or prolonged)	25JUL2019 / 27JUL2019	Severe	Not related	Probable	Medical therapy	Completely recovered/ Resolved	02AUG2019
01-014	26OCT2019 / 04NOV2019	Urosepsis; patient was found unresponsive, with a fever, also with a possible hypocortisole crisis. During her admission E.Coli bacteria were found. And she was succesfully treated with antibiotics.	Yes	Serious deterioration in the health of the subject		Hospitalization (initial or prolonged), Medical/surgical intervention to prevent life threatening illness or injury or permanent impairment	26OCT2019 / 01NOV2019	Severe	Not related	Not related	Medical therapy	Completely recovered/ Resolved	04NOV2019
01-014	30OCT2019 / 01NOV2019	High sodium	Yes	Serious deterioration in the health of the subject		Hospitalization (initial or prolonged)	26OCT2019 / 01NOV2019	Moderate	Not related	Probable	Medical therapy	Completely recovered/ Resolved	01NOV2019

[a] SAE = Serious adverse event

[b] all criteria for serious adverse event that apply

[c] if serious adverse event is death

Patient ID	Start / End date	AE description	SAE? [a]	SAE criteria [b]	Date / cause of death [c]	Serious deterioration in health resulted in:	If hospitalized, date of admission / discharge	Severity	Device related	Procedure related	Action taken	AE outcome	Date of resolution / stabilization
01-014	31JAN2019 / Ongoing	panhypopituitarism: which is expressed in::'Endocrinologic dysfunction: panhypopituitarism with loss of thyrotrope, gonadotrope and corticotrope axis, electrolyte disturbances, diabetes insipidus	Yes	Serious deterioration in the health of the subject		Life-threatening illness or injury, Hospitalization (initial or prolonged), Permanent impairment of a body structure or a body function	29JAN2019 / 12FEB2019	Severe	Not related	Probable	Medical therapy	Ongoing	21FEB2020
01-014	30JAN2019 / Ongoing	Hypothalaam syndrome with disturbed temperature regulation	Yes	Serious deterioration in the health of the subject		Hospitalization (initial or prolonged), Permanent impairment of a body structure or a body function	29JAN2019 / 12FEB2019	Severe	Unlikely	Probable	None	Ongoing	21FEB2020
01-015	03MAR2019 / 08MAY2019	Sub dural Hematoma	Yes	Serious deterioration in the health of the subject		Hospitalization (initial or prolonged)	03MAR2019 / 06MAR2019	Moderate	Unlikely	Probable	None	Completely recovered/ Resolved	08MAY2019
01-015	03MAR2019 / 06MAR2019	Epilepsy	Yes	Serious deterioration in the health of the subject		Hospitalization (initial or prolonged)	03MAR2019 / 06MAR2019	Moderate	Unlikely	Probable	Medical therapy	Completely recovered/ Resolved	06MAR2019

[a] SAE = Serious adverse event

[b] all criteria for serious adverse event that apply

[c] if serious adverse event is death

Patient ID	Start / End date	AE description	SAE? [a]	SAE criteria [b]	Date / cause of death [c]	Serious deterioration in health resulted in:	If hospitalized, date of admission / discharge	Severity	Device related	Procedure related	Action taken	AE outcome	Date of resolution / stabilization
01-022	28MAR2019 / 10APR2019	Chemical meningitis + Hydrocephalus	Yes	Serious deterioration in the health of the subject		Hospitalization (initial or prolonged), Medical/surgical intervention to prevent life threatening illness or injury or permanent impairment	19MAR2019 / 12APR2019	Moderate	Possible	Probable	Medical therapy	Completely recovered/ Resolved	10APR2019
01-022	31JUL2019 / 01AUG2019	anafalactic shock when given IV amfo B	Yes	Serious deterioration in the health of the subject		Medical/surgical intervention to prevent life threatening illness or injury or permanent impairment		Severe	Not related	Not related	Medical therapy	Completely recovered/ Resolved	01AUG2019
01-022	10JUL2019 / 25MAR2020	(recurrent) Viral eye infection. which caused decreased vision, acute retinal necrosis and was treated with vitrectomy and laser therapy	Yes	Serious deterioration in the health of the subject		Hospitalization (initial or prolonged), Permanent impairment of a body structure or a body function, Medical/surgical intervention to prevent life threatening illness or injury or permanent impairment	31JUL2019 / 14AUG2019	Severe	Unlikely	Possible	Medical therapy	Recovered/ Resolved with sequelae	

[a] SAE = Serious adverse event

[b] all criteria for serious adverse event that apply

[c] if serious adverse event is death

Patient ID	Start / End date	AE description	SAE? [a]	SAE criteria [b]	Date / cause of death [c]	Serious deterioration in health resulted in:	If hospitalized, date of admission / discharge	Severity	Device related	Procedure related	Action taken	AE outcome	Date of resolution / stabilization
02-009	25MAR2020 / 31MAR2020	appendicitis	Yes	Serious deterioration in the health of the subject		Hospitalization (initial or prolonged), Medical/surgical intervention to prevent life threatening illness or injury or permanent impairment		Severe	Not related	Not related	Medical therapy, Surgical intervention	Completely recovered/ Resolved	31MAR2020
02-009	14APR2020 / 17APR2020	Abcess appendix removal site	Yes	Serious deterioration in the health of the subject		Hospitalization (initial or prolonged), Medical/surgical intervention to prevent life threatening illness or injury or permanent impairment	14APR2020 / 17APR2020	Severe	Not related		Medical therapy, drain placed	Completely recovered/ Resolved	17APR2020

[a] SAE = Serious adverse event

[b] all criteria for serious adverse event that apply

[c] if serious adverse event is death