Clinical Trial Protocol: 3599-001

Study Title:	A Randomised Controlled Study to Evaluate the Efficacy and Safety of Fibrin Sealant, Vapour Heated, Solvent/Detergent Treated (FS VH S/D 500 s-apr) Compared to DuraSeal Dural Sealant as an Adjunct to Sutured Dural Repair in Cranial Surgery.
Study Number:	3599-001
Study Phase:	Phase 3
Product Name:	Fibrin sealant, vapour heated, solvent/detergent, 500 IU/mL thrombin, synthetic aprotinin, frozen (referred to as FS VH S/D 500 s-apr in this protocol)
IND Number:	013204
EudraCT Number	2015-005535-40 ClinicalTrials.gov Identifier: NCT02891070
Indication:	The use of FS VH S/D 500 s-apr as an adjunct to suture repair sealing in dura mater closure
Investigators:	Multicenter study
Sponsor:	Baxter Healthcare Corporation One Baxter Parkway Deerfield, Illinois 60015, USA
Sponsor Contact:	[redacted] Baxter Healthcare Corporation Clinical & HEOR, Global Science & Technology Holger-Crafoord-Straße 26 72379 Hechingen, Germany Phone: [redacted]
Sponsor's EU Legal Representative:	[redacted] Baxter R&D Europe SPRL Boulevard René Branquart 80 7860 Lessines, Belgium
Medical Monitor:	[redacted] Baxter Healthcare Corporation Clinical & HEOR, Global Science & Technology 25212 W. IL. Route 120, RTL-10 Round Lake, Illinois 60073, USA

	Date
Original Protocol:	12 Apr 2016
Amendment 1:	14 Apr 2016
Amendment 2:	06 Nov 2017

Confidentiality Statement

[redacted]

SYNOPSIS

Sponsor:

Baxter Healthcare Corporation

Name of Finished Product:
Fibrin sealant, vapour heated, solvent/detergent, 500 IU/mL thrombin, synthetic aprotinin, frozen (referred to as FS VH S/D 500 s-apr in this synopsis).

Name of Active Ingredient:

Test product: Fibrinogen (human), thrombin (human), aprotinin (synthetic), and calcium chloride.

Control device: Polyethylene glycol (PEG) ester solution, and trilysine amine solution.

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

Study Number:
3599-001

Study Phase: Phase 3

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

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

Study Design:
This study is a Phase 3, prospective, controlled, randomised, single-blind (patient), multicenter study to evaluate the safety and efficacy of FS VH S/D 500 s-apr compared to DuraSeal Dural Sealant as an adjunct to sutured dural closure in a total of 202 evaluable patients undergoing elective cranial surgery for the treatment of a pathological condition (eg, benign/malignant tumours, vascular malformations, or Chiari type 1 malformations) specifically located in the posterior fossa (PF) or supratentorial (ST) regions.

Eligible patients will sign an informed consent (IC), and undergo elective cranial surgery of the PF or ST region with either craniotomy or craniectomy with planned durotomy. During the surgery, the patients will be evaluated according to intra-operative inclusion/exclusion criteria for further eligibility. If eligible, the patients will be evaluated upon completion of the primary suturing of the dura (with or without non-autologous duraplasty or autologous tissue). Only if intra-operative cerebrospinal fluid (CSF) leak is confirmed (spontaneous CSF leak or CSF leak after Valsalva manoeuvre; 25 cm H_2O for up to 5 - 10 seconds), the patient will be randomised to treatment with either FS VH S/D 500 s-apr or DuraSeal Dural Sealant (control) in a 1:1 allocation ratio stratified by center and surgical regions (PF or ST). After treatment, a final assessment for intra-operative CSF leak (spontaneous CSF leak or CSF leak after Valsalva manoeuvre) will be conducted to evaluate the intra-operative watertight dura closure.

Two applications of the study products are allowed. In the event that 2 applications are used, the Valsalva manoeuvre must be repeated. In the case of continuous intra-operative CSF leak at the final assessment, a rescue therapy for sealing any CSF leaks may be applied according to the surgeon's choice/institutional practice (eg, other fibrin sealants [FSs] except FS VH S/D 500 s-apr or DuraSeal Dural Sealant).

Study Population:
Approximately 476 patients will be screened in order to randomise approximately 224 patients (with a minimal number of 56 PF procedures) and have 202 evaluable patients age ≥18 years, both genders, to

undergo elective craniotomy/craniectomy for pathological processes in the PF or ST region (eg, benign or malignant tumours, vascular malformation, or Chiari type 1 malformations) and who were demonstrated to have persistent CSF leakage following the completion of primary closure of the dural incision will be enrolled in this study.

The study will be conducted in 4 countries (United States, Spain, Germany, and Czech Republic). Additional countries may be involved in the trial.

Test Product and Dose:
FS VH S/D 500 s-apr frozen 4 mL syringe

Mode of administration:

FS VH S/D 500 s-apr will be applied to the sutured dural line on a dry surface. Two applications will be allowed in order to obtain watertight sealing of suture line.

The neurosurgical procedures will be performed according to the standard practices applicable to each indication. The dura will be closed with suture types and needle sizes according to the surgeon's preference. Special care will be taken to ensure that if tenting sutures are used, they do not perforate the dura. Patients having gaps/defects between dura edges that are >2 mm after primary suturing will be excluded due to the limitations of FS VH S/D 500 s-apr.

FS VH S/D 500 s-apr will be prepared according to the protocol and applied in a thin layer with 5 mm on each side of the suture line ensuring that all suture holes are covered.

Approximately 2 mL of FS VH S/D 500 s-apr will be used to cover a suture line 10 cm long and 1 cm wide (10 cm^2), as per the package insert. After application of FS VH S/D 500 s-apr, the surgeon will wait 3 minutes before testing for CSF leak in order to achieve sufficient polymerization.

In the control group, DuraSeal Dural Sealant will be prepared and applied according to the instructions in the protocol appendix.

Duration of Treatment:
The patient's continuation in the clinical study is defined at randomisation and ends upon completion of the scheduled final Follow-up visit on post-operative Day 60 (±3 days). According to clinical experience, the incidence of CSF leaks are rare, however when they do occur the majority are detected within 60 days. Therefore, the follow-up period is deemed appropriate. The period between enrolment (i.e., signed IC) and surgery will not exceed 30 days; screening procedure results are valid for 30 days. After 30 days, the laboratory tests, the review of systems, and the physical examination must be repeated. Post-operative follow-up visits are scheduled to take place on the day before discharge or on post-operative Day 5 (±2 days), whichever is first, on post-operative Day 30 (±3 days), and on post-operative Day 60 (±3 days) (last study visit), and safety evaluations will be recorded during this time period including post-operative CSF leaks (clinical observation, diagnostic testing, or need for surgical intervention to treat CSF leak or pseudomeningocele)**.**

Assessments:
<u>Primary efficacy assessments</u>

The primary assessment is the proportion of patients who have neither of the following:

Intra-operative CSF leakage from dural repair after up to two FS VH S/D 500 s-apr/control applications during Valsalva manoeuvre (25 cm H2O for up to 5 - 10 seconds)

Post-operative CSF leakage within 30 (+3) days post-operatively

<u>Secondary efficacy assessments</u>

- Incidence of intra-operative CSF leakage following final Valsalva manoeuvre
- Incidence of CSF leaks within 30 (+3) days post-operatively
- Time in surgery (minutes)
- Time from dural closure (application of investigational product) until end of surgery
- Length of stay in hospital (days)

Safety Assessments:

- Incidence of CSF leaks within 60 (+3) days post-operatively
- Incidence of adverse events (AEs) up to 60 (+3) days post-operatively
- Incidence of surgical site infections (SSIs) according to the United States (US) National Healthcare Safety Network (NHSN) within 30 (+3) days post-operatively
- Number of unplanned interventions within 30 (+3) days post-operatively
- Abnormal laboratory values and vital signs (e.g., elevated white blood cell [WBC] count, fever [temperature >100.7°F or 38.2°C], tachycardia [pulse >100], hypotension [mean arterial pressure <60])

Statistical Methods:

Sample Size Calculation:

In this non-inferiority (NI) study, the proportions of patients meeting the composite primary endpoint are assumed to be [redacted]% for FS VH S/D 500 s-apr and [redacted]% for DuraSeal Dural Sealant; the NI margin is defined as 10%, the 1-sided Type 1 error rate (α) is 2.5%, the statistical power (1-β) is 80%. One interim analysis after 50% of patients complete the study is assumed, resulting in an overall sample size of 202 evaluable patients. To reach this number, 112 patients will be randomised to each treatment group (ie, 224 total patients)

Planned Statistical Analysis:

Primary efficacy endpoint analysis:

The primary composite efficacy endpoint, proportion of patients not meeting the 2 criteria (ie, no intra-operative CSF leakage and no post-operative CSF leakage), will be investigated by a 2-sided test for non-inferiority using logistic regression, taking into account the following covariates: study center and surgery region. Non-inferiority of FS VH S/D 500 s-apr to DuraSeal Dural Sealant will be assessed using the confidence interval approach and a NI margin of 10%.

Secondary efficacy endpoint analyses:

The logistic regression approach used for the primary efficacy endpoint will also be used to calculate the proportions of: incidence of intra-operative CSF leakage following final Valsalva manoeuver and the incidence of CSF leaks within 30 (+3).

The time in surgery, time from dural closure until the end of surgery, and the length of stay in hospital will be compared between the 2 treatment groups using a Wilcoxon rank sum test.

Safety endpoint analyses:

The logistic regression approach used for the primary endpoint will also be used to calculate the proportions of: incidence of CSF leaks within 60 (±3) days post-operatively, and incidence of SSIs according to NHSN within 30 (±3) days post-operatively.

The number of unplanned interventions within 30 (±3) days post-operatively will be compared between the 2 treatment groups using a Wilcoxon rank sum test.

Listings will be prepared for laboratory results and vital signs.

Date of Protocol Amendment 2: 06 Nov 2017

Prepared in: Microsoft Word 2013

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LIST OF ABBREVIATIONS AND TERMS

AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Advanced Syringe Technology
B19V	Parvovirus B19
BUN	Blood urea nitrogen
CBGB	Coronary artery bypass grafting surgery
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CRO	Contract research organisation
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for AEs
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EU	European Union
EudraCT	EudraPharm Clinical Trial
FAS	Full analysis set
FS	Fibrin Sealant
GCP	Good Clinical Practice
HAV	Hepatitis A virus
HbA1c	Glycated haemoglobin
HBV	Hepatitis B virus
Hct	Haematocrit
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
Hgb	Haemoglobin
IB	Investigator's Brochure
IC	Informed consent
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICP	Intracranial pressure

ICU	Intensive care unit
IND	Investigational new drug
INR	International normalised ratio
IP	Investigational product
IRB	Institutional Review Board
IWRS	Interactive Web-response system
MedDRA	Medical Dictionary for Regulatory Activities
MRP	Mutual Recognition Procedure
N	Number of patients
NCA	National Competent Authority
NHSN	National Healthcare Safety Network
NI	Non-inferiority
NMC	Non-medical complaint
OR	Odds ratio
PEG	Polyethylene glycol
PF	Posterior fossa
PIC	Patient identification code
PPS	Per protocol set
RCT	Randomised controlled trial
RNA	Ribonucleic acid
RBC	Red blood cell
RR	Relative risk
SAE	Serious adverse event
SAER	Serious adverse event report
S/D	Solvent/detergent
SmPC	Summary of Product Characteristics
SSI	Surgical site infections
ST	Supratentorial
ULN	Upper limit of normal
US	United States
VH	Vapour heat
Y/N	Yes/No
WBC	White blood cell

PR interval	The interval that extends from the beginning of the P wave (the onset of atrial depolarization) until the beginning of the QRS complex
QRS	Ventricular depolarization
QT interval	The measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle.

1. INTRODUCTION

1.1 Background

In neurosurgery, cerebrospinal fluid (CSF) leaks where disruption of the arachnoid and the dura mater allows CSF to flow to an extradural space, is an event which may lead to severe complications, such as infection, pseudomeningocele, and delayed pneumocephalus. Closure of the dura serves as a mechanical and a biological barrier to both CSF leaks and to the potential entrance of infectious organisms. Reported incidences of post-operative CSF leaks may vary on average from 0.8 to 13%, depending on the type of surgery and other factors. Craniotomy and craniectomy in the posterior fossa (PF) region may have post-operative CSF leaks ranging from 2% to 11.5%, respectively.[1-4] Cerebrospinal fluid leak rates are reported to be lower in the supratentorial (ST) region (6.3%) and during smaller trans-sphenoidal procedures (6.8%), but are much higher in infratentorial procedures and extensive skull base procedures (12.8% and 34.6%, respectively).[5]

Persisting CSF leaks may result in post-operative meningitis in about 3.1% of interventions with a mean onset of 12 days after surgery.[6] The relative risk (RR) for developing meningitis in patients with post-operative CSF leak is increased to a RR = 10.[6]

Also, the risk of surgical site infections (SSIs) is increased in patients with a post-operative CSF leak with an odds ratio (OR) for SSI of 3.5 (95% CI 1.4 - 8.5), leading to increased length of stay in the hospital.[7] Risk factors for CSF leaks after 545 cranial surgeries were surgery in the PF region, opened pneumatised spaces, age, size of craniotomy, craniectomies, large remaining dural defects, wound closure without using muscle sutures, and suture techniques.[8] Post-operative CSF leaks will, in most cases, eventually cease spontaneously or will heal under conservative management including lumbar drainage or with medical treatment to lower the intracranial pressure (ICP). Patients who do not respond to conservative/medical treatment may require surgical revision to close the persisting CSF leak, introducing discomfort to the patient and increased overall costs. In fact, neurosurgical procedures with CSF leaks in 1 study increased costs by 141% over procedures that did not have CSF leaks.[5]

The first attempt to treat and control CSF leaks is done by the neurosurgeon at the end of the surgical intervention when the dural edges are to be closed. The goal is a watertight closure of the dura. Defects or large dural gaps might require use of different patches/grafts such as autograft, allograft, xenograft, or synthetic grafts.[9-16] If the dura edges can be met, meticulous suturing of the dura is important to gain a watertight

closure and suturing is considered standard of care by neurosurgeons. However, with increased ICP, CSF may leak through even small suture holes in the dura, causing a persisting CSF leak often already detected during surgery. Regardless of how meticulously dura suturing is performed, intra-operative CSF leakage has been shown to persist in most patients at a CSF opening pressure >20 cm H_2O.[17] A pressure of 20 cm H_2O (equal to 10 - 15 mm Hg) is considered the upper limit of a physiological ICP and can easily be exceeded at times (eg, coughing) and can be increased during surgery using the Valsalva manoeuvre.[18]

To minimize the risk of intra-operative CSF leaks and to potentially reduce post-operative CSF leak rates, different techniques and materials have been used in conjunction to sutures to provide a watertight sealing of the dural incision; one such treatment modality is the use of a fibrin sealant (FS) directly on the suture line to seal the suture holes, as well as the approximated dural edge (as long as the gap is <2 mm wide). [9-16] Fibrin sealants consist of a group of compounds with 2 main active ingredients, fibrinogen and thrombin, that, when mixed, form a fibrin clot. Fibrin sealants applied to tissue during surgery have 4 main functions: haemostasis, tissue sealing, tissue adhesion, and wound healing.[19] These FSs may be in liquid form (eg, Tisseel, Tissucol) or as a part of a dry patch.[20]

The FS that has been available for the longest time to clinicians in both Europe (since 1978) and the United States (US; since 1998) is Tisseel (Fibrin Sealant, Vapour Heated, Solvent/Detergent Treated 500 synthetic aprotinin [FS VH S/D 500 s-apr], Baxter Healthcare Corporation [Baxter], Deerfield, IL, US). Several generations of FSs up to the current product FS VH S/D 500 s-apr have been developed, mainly focusing on improving the viral safety and handling properties of the product. Thus, the latest FS generation FS VH S/D 500 s-apr comprises 2 dedicated virus inactivation steps (ie, vapour heat [VH] treatment and solvent/detergent [S/D] treatment), in the manufacture of both human plasma-derived product components (fibrinogen and thrombin component). Vapour heat is effective in inactivation of lipid-enveloped ribonucleic acid (RNA) viruses, such as human immunodeficiency virus (HIV), lipid-enveloped double-stranded deoxyribonucleic acid viruses such as pseudorabies virus, and non-enveloped RNA viruses such as hepatitis A virus (HAV), while S/D treatment is effective against lipid-enveloped RNA and deoxyribonucleic acid viruses, for example hepatitis C virus (HCV) and hepatitis B virus (HBV). The main indications for use in the European Union (EU) as supportive treatment adjunct to standard surgical techniques are to improve haemostasis, to improve wound healing, and to support sutures in vascular surgery and gastrointestinal anastomoses and for tissue sealing.[19]

1.2 Description of Investigational Product

The Investigational Product (IP) for this protocol is FS VH S/D 500 s-apr in its frozen presentation.

FS VH S/D 500 s-apr is a 2-component FS made from pooled human plasma. When combined, the 2 components, fibrinogen (human) and thrombin (human), mimic the final stage of the blood coagulation cascade.

Fibrinogen (human) is a sterile, non-pyrogenic, VH- and S/D-treated preparation made from pooled human plasma. It is provided as a frozen solution pre-filled into 1 side of a dual-chambered syringe (eg, Advanced Syringe Technology [AST]). The main active ingredient in the fibrinogen component is human fibrinogen (as clottable protein 91 mg/mL) contained in a total protein concentration of 96 - 125 mg/mL.[19] A fibrinolysis inhibitor, aprotinin (synthetic, 3000 KIU[1]/mL), is included in the fibrinogen component to delay fibrinolysis. Other ingredients include: human albumin, L-histidine, niacinamide, sodium citrate dihydrate, polysorbate 80 (Tween 80) (0.6 - 1.9 mg/mL), and water for injections.

Thrombin (human) is a sterile, non-pyrogenic, VH- and S/D-treated preparation made from pooled human plasma. It is provided as a frozen solution pre-filled into 1 side of a dual-chambered syringe (eg, AST). The thrombin component contains the clotting activator thrombin (human, 500 IU[2]/mL) and calcium chloride (40 µmol/mL). Other ingredients are: human albumin, sodium chloride, and water for injections.

FS VH S/D 500 s-apr contains plasminogen, fibronectin, and factor XIII as process-related substances. In some countries, factor XIII is classified as an active ingredient.

The use of FS VH S/D 500 s-apr is only topical (application by drip) to cover the dura suture line in order to work as a sealant.

A detailed description of the study product is provided in the Summary of Product Characteristics (SmPC)[19] of the Mutual Recognition Procedure (MRP) and the US Prescribing Information.[20]

[1] 1 EPU (European Pharmacopoeia Unit) corresponds to 1800 KIU (Kallidinogenase Inactivator Unit).
[2] Thrombin activity is determined using the current WHO Standard for thrombin.

1.2.1 Approved Therapeutic Indications

In the EU MRP, according to the SmPC,[19] FS VH S/D 500 s-apr is approved for supportive treatment where standard surgical techniques appear insufficient:

- For improvement of haemostasis.
- As a tissue glue to improve wound healing or to support sutures in vascular surgery and in gastrointestinal anastomoses.
- For tissue sealing, to improve adhesion of the separated tissue (e.g., tissue flaps, grafts, split skin grafts [mesh grafts]).

The efficacy in fully heparinised patients has been proven.

In the US, according to the prescribing information,[20] the therapeutic indications for FS VH S/D 500 s-apr are:

- For use as an adjunct to hemostasis in adult and pediatric patients (>1 month of age) undergoing surgery when control of bleeding by conventional surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. FS VH S/D 500 s-apr is effective in heparinised patients.
- As a FS indicated as an adjunct to standard surgical techniques (such as suture and ligature) to prevent leakage from colonic anastomoses following the reversal of temporary colostomies.

1.2.2 Contraindications

Known hypersensitivity to any constituents of the product, including aprotinin.[21]

1.3 Clinical Condition/Indication

In this protocol, FS VH S/D 500 s-apr is intended to be used as an adjunct to sutured dural repair in cranial surgery in patients undergoing elective cranial surgery for the treatment of a pathological condition (eg, benign/malignant tumours, vascular malformations, or Chiari type 1 malformations) specifically located in the PF or ST regions.

1.4 Evaluation of Anticipated Risks and Benefits of the IP to Humans

The efficacy and safety of Baxter's FSs have also been demonstrated in post-marketing experience, as Baxter's FSs have been commercialised for more than 30 years (also for

neurosurgery indication in many countries), with a positive benefit-risk balance, which is documented in periodic benefit-risk evaluation reports according to EU and US regulations. No safety signal has been identified from the reports on use in neurosurgical procedures in the EU; note that there is no neurosurgical procedure indication in the US.[20]

In this clinical trial, the product will be used according to this protocol and to the specifications outlined in the current Investigator's Brochure (IB) to minimize any risks. No increased adverse event (AE) risk has been identified over control treatments in the previous clinical trials conducted with the IP. [22] For general information about safety of plasma-derived products, please see the IB. With correct handling and application technique of the IP, as described in this protocol and in the IB, the anticipated risks to the patients in this clinical trial are expected to be minimal. The expected benefit of the IP is to provide watertight CSF closure to the suture line and potentially reduce complications for the patients due to CSF leaks after the surgical intervention.[23,24] These anticipated benefits seem to outweigh the potential and minimal risks associated with the use of the IP (see the IB for additional details).

2. STUDY OBJECTIVES

The purpose of this study is to provide data on the safety and efficacy of FS VH S/D 500 s-apr compared to DuraSeal Dural Sealant as an adjunct to sutured dural closure in patients who are undergoing elective cranial surgery for the treatment of a pathological condition (eg, benign/malignant tumours, vascular malformations, or Chiari type 1 malformations) specifically in the PF or ST region.

2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of FS VH S/D 500 s-apr compared to DuraSeal Dural Sealant as an adjunct to sutured dural closure.

2.2 Secondary Objective

The secondary objective of this study is to evaluate the safety of FS VH S/D 500 s-apr compared to DuraSeal Dural Sealant as an adjunct to sutured dural closure.

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This study is a Phase 3, prospective, controlled, randomised, single-blind (patient), multicenter study to evaluate the safety and efficacy of FS VH S/D 500 s-apr compared to DuraSeal Dural Sealant as an adjunct to sutured dural closure in a total of 202 evaluable patients undergoing elective cranial surgery for the treatment of a pathological condition (i.e., benign/malignant tumours, vascular malformations, or Chiari type 1 malformations) specifically located in the PF or ST region.

Eligibility according to general and intra-operative criteria will lead to the final selection of the patient into the study, which is determined by the presence of an intra-operative CSF leak after primary dural closure with sutures. Upon detection of CSF leak, the patient's randomisation assignment to either IP (FS VH S/D 500 s-apr) or to control (DuraSeal Dural Sealant) stratified by center and surgical regions (PF or ST) will be applied.

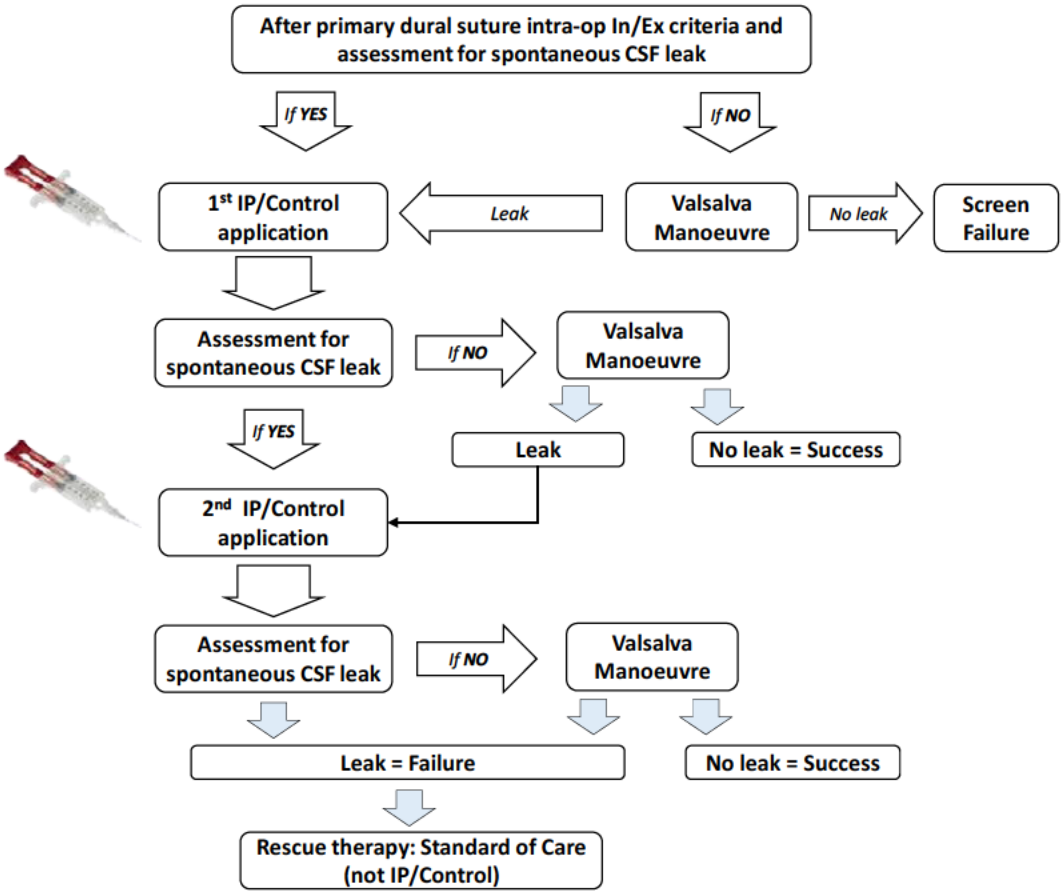
3.2 Overall Study Design

Patients who are ≥18 years of age who sign the informed consent (IC) and who meet all pre-operative inclusion/exclusion criteria will undergo elective cranial surgery with either craniotomy or craniectomy with planned durotomy. Their eligibility for surgery will be evaluated on the basis of the routine medical work-up (medical history, physical examination/review of systems, laboratory, imaging) and of the screening results for general inclusion and exclusion criteria (Section 4.2) during the ≤30-day period prior to surgery.

For a schematic diagram of intra-operative study design, see Figure 1. During surgery (Day 0), patients will be evaluated according to intra-operative inclusion and exclusion criteria for further eligibility (Section 4.3); if eligible, patients will be evaluated upon completion of the primary suturing of the dura. Only if an intra-operative CSF leak is observed (spontaneous CSF leak or CSF leak after Valsalva manoeuvre; 25 cm H_2O for up to 5 - 10 seconds), the patient's randomisation assignment to 1 of 2 treatments – repair with FS VH S/D 500 s-apr or DuraSeal Dural Sealant as an adjunct to dural closure – will be applied. Patients with no intra-operative CSF leak will not be enrolled in the trial (ie, defined as screen failures).

See Appendix 1 (Schedule of Procedures and Assessments).

Figure 1. Intra-operative Study Design



3.3 Rationale for Study Design and Control Group

With the specific properties of liquid FS VH S/D 500 s-apr (ie, tissue adhesion, sealing, wound healing) when combined with appropriate suture techniques, the potential benefit in the creation of a watertight suture line in the dura mater for patients undergoing neurosurgery seems logical and clinically relevant. Though current and previous generations of FS VH S/D 500 s-apr have been used extensively as an adjunct to suturing in dural repair for many years, this study will compare the use of FS VH S/D 500 s-apr to the use of DuraSeal Dural Sealant as an adjunct in dural repair. Additionally, the European Guideline on Core SmPC for Plasma-derived FS/Haemostatic Products requires clinical data to support any indication for the sealing of the dura suture line during cranial surgery.[25]

The only clinical study data for FS VH S/D 500 s-apr is from a small randomised controlled trial (RCT) pilot study (N = 62) conducted by Baxter, where FS VH S/D 500 s-apr was used to augment the closure of a dura defect by suturing in a patch of autologous fascia, pericranium or suturable collagen-based dura substitute, which was the standard of care. The primary endpoint was the incidence of post-operative CSF leak at 33 days post-operatively. The results demonstrated no disadvantage with adding FS VH S/D 500 s-apr to the standard of care; safety was also shown to be comparable to standard of care. During this study, cranial surgery was specifically located in the PF region. CSF leakage after primary dura sutures was excluded. It is important to note that though the results demonstrated no disadvantage using FS VH S/D 500 s-apr as a sealant, the study was very small and likely underpowered to demonstrate any superiority effect; thus the study was considered inconclusive. However, FS VH S/D 500 s-apr was demonstrated to be safe for neurosurgery.

Recently, a large (n = 139) and well-powered RCT was conducted. The RCT evaluated a similar FS product, containing the same main active ingredients (fibrinogen and thrombin) as FS VH S/D 500 s-apr; this study proved superiority of another FS over the control treatment (sutures only) in providing a watertight dural closure during surgery.[26] The safety profile was comparable in the 2 groups and, with this trial, an indication for "suture line sealing in dura mater closure" was obtained in the EU.

Baxter believes that FS VH S/D 500 s-apr will perform equivalently to the DuraSeal Dural Sealant when used as an adjunct to suturing during surgery. While other clinical designs were discussed, the design chosen seems appropriate, as it provides a reasonably accurate reflection of the typical usage of FS in clinical practice.

3.4 Study Duration and Dates

The overall duration of the study is expected to be 26 months from study initiation (ie, first patient enrolled) to study completion (ie, last patient last visit). The recruitment period is expected to be 24 months.

The patient participation period is from pre-operative screening to Day 60 (±3 days) after surgery (ie, last study visit), unless prematurely discontinued.

Day of surgery is defined as Day 0. Scheduled Follow-up visits (Appendix 1) will take place on the day before discharge or on Day 5 (±2 days), whichever is first, Day 30 (±3 days), and on Day 60 (±3 days) after surgery (last study visit). Follow-up visits will be advanced if complications occur prior to the scheduled date. According to clinical

experience, the incidence of CSF leaks are rare, however when they do occur the majority are detected within 60 days. Therefore, the follow-up period is deemed appropriate.

Patients are strongly encouraged to contact or visit the study site without delay to discuss a perceived AE that occurs after the first Follow-up visit and between the scheduled Follow-up visits, and to follow the directives of the study site for appropriate action (Unscheduled Follow-up visit assessments, see Appendix 1).

See schematic study overview including the study visits (Days 0, 5, 30, and 60) in Appendix 1.

4. STUDY POPULATION SELECTION

4.1 Study Population

Approximately 476 patients will be screened in order to randomise approximately 224 patients (with a minimal number of 56 PF procedures) and have 202 evaluable patients age ≥18 years, both genders, who are to undergo elective craniotomy/craniectomy for pathological processes (eg, benign or malignant tumours, vascular malformation, or Chiari type 1 malformations) in the PF or ST region and who have persistent CSF leakage following the primary attempt at suture closure of the dural incision. Randomisation will be stratified by study center and surgical region (PF or ST) and will be aimed to achieve an approximate 3:1 ratio (ST:PF) of the 2 surgical regions in the randomised study population. The minimal number of PF procedures will be approximately 56.

We have estimated a [redacted]% screen failure rate, based on published literature, using a similar method to detect CSF leaks during cranial surgery.[27]

The study will be conducted in 4 countries (US, Spain, Germany, and Czech Republic). Additional countries may be involved in the trial.

4.2 Inclusion and Exclusion Criteria (General)

The general inclusion criteria (1 - 5) and the general exclusion criteria (1 - 20) are to be evaluated before each patient undergoes planned surgery. Only patients who meet the general inclusion criteria and do not meet the general exclusion criteria are to be evaluated further according to the intra-operative inclusion and exclusion criteria Section 4.3.

4.2.1 Inclusion Criteria (General)

Each patient must meet the following criteria to be enrolled in this study. Any patient not meeting all the inclusion criteria will be regarded as a screen failure.

1. Patients ≥18 years of age undergoing craniotomy/craniectomy for pathological processes in the PF or ST region
2. Patients must be willing and able to participate in the study and provide written IC before any protocol specific assessment is performed
3. Patients must be willing to receive peri-operative antibiotic prophylaxis
4. Female patients of childbearing potential must present with a negative serum pregnancy test, and must agree to employ adequate birth control measures

[restricted to abstinence, barrier contraceptives, intrauterine contraceptive devices or licensed hormonal products] for the duration of their participation in the study

5. Patients are willing and able to comply with the requirements of the protocol

4.2.2 Exclusion Criteria (General)

Each patient must not meet the following criteria to be enrolled in this study. Any excluded patient will be regarded as a screen failure.

1. Patients with a dural lesion from a recent surgery that still has the potential for CSF leakage
2. Patients who had undergone chemotherapy treatment, excluding hormonal therapy, within 3 weeks prior to the planned procedure, or with chemotherapy scheduled within 7 days following surgery
3. Patients with radiation therapy to the surgical site or standard fractionated radiation therapy scheduled within 7 days following surgery
4. Patients with a previous craniotomy/craniectomy within 6 months prior to the study surgery
5. Use of corticosteroids on a chronic basis (defined as daily use of corticosteroids for ≥8 weeks) for purposes other than decreasing the symptoms of systemic chemotherapy (unless if those steroids were discontinued 4 weeks prior to the planned surgery)
6. Patients with a known hypersensitivity to the components of the IP or control (human fibrinogen, synthetic aprotinin, human albumin, human FXIII, tri-sodium citrate, histidine, niacinamide, polysorbate 80, human thrombin, polyethylene glycol [PEG], trilysine amine)
7. Patients with a known hypersensitivity to US Federal Drug & Cosmetic Blue #1 dye
8. Evidence of an infection indicated by any one of the following: clinical examination supporting the diagnosis of infection, fever (temperature >100.7°F or 38.2°C), positive urine culture, positive blood culture, positive chest X-ray consistent with pulmonary infection, or infection along the planned surgical path. A white blood cell (WBC) count of <20000 cells/µL is permitted if the patient is being treated with steroids in the absence of all other infection parameters

9. Female patients of childbearing potential with a positive pregnancy test or intent to become pregnant during the clinical study period
10. Female patients who are nursing
11. Patients with exposure to another investigational drug or device clinical trial within 30 days prior to enrolment or anticipated in the 60-day Follow-up period
12. Patients with severely altered renal function as confirmed by local laboratory reference ranges for serum creatinine and/or hepatic function (alanine aminotransferase [ALT], aspartate aminotransferase >3 × upper limit of normal [ULN])
13. Patients who currently have or have had a compromised immune system (such as Acquired Immune Deficiency Syndrome [AIDS]) or autoimmune disease, or were on chronic immunosuppressant agents
14. Patients with uncontrolled diabetes as evidenced by the institution's standard of care (glycated haemoglobin [HbA1c] >7%, blood glucose, etc.)
15. Patients with traumatic injuries to the head
16. Patients with dural injury during craniotomy/craniectomy that cannot be eliminated by widening the craniotomy/craniectomy to recreate the native dural cuff
17. Patients requiring surgical approaches that would not allow sutured dural closure such as trans-sphenoidal or translabyrinthine/-petrosal/-mastoid. Superficial penetration of mastoid air cells is allowed
18. Patients with hydrocephalus, except occlusive hydrocephalus caused by PF pathology or incompletely open cerebrospinal fluid pathways, to be treated during surgical procedure
19. Existing CSF (ventricular, etc.) drains, Cushing/Dandy cannulation, or Burr holes which damage the dura
20. Patients with confined bony structures where nerves are present and neural compression may result due to swelling

4.3 Inclusion and Exclusion Criteria (Intra-operative)

The intra-operative inclusion criteria (1 - 3) and the intra-operative exclusion criteria (1 - 9) will be evaluated when the patient is in surgery.

4.3.1 Inclusion Criteria (Intra-operative)

1. Patients with surgical wound classification Class I (Appendix 3)
2. The cuff of native dura along the craniotomy edge on each side is adequate, based on surgeon's judgment, to facilitate suturing and to allow for sufficient surface area for adherence of the IP
3. Patient's CSF leak was present intra-operatively following completion of primary dural closure (with or without non-autologous duraplasty or autologous tissue); either spontaneously or upon Valsalva manoeuver (25 cm H_2O for up to 5 - 10 seconds)

4.3.2 Exclusion Criteria (Intra-operative)

1. Patient has a gap between durotomy edges of >2 mm after primary dural closure in the judgment of the investigator
2. Patients requiring the use of implants made of synthetic materials coming into direct contact with dura
3. Patient has 2 or more separate dural defects
4. Patients with intersecting durotomy scars in the surgical path from a previous operation that cannot be completely removed by the planned dural resection
5. Placement of Gliadel Wafers
6. Major intra-operative complications that require resuscitation or deviation from the planned surgical procedure
7. Patients in whom application of the Valsalva manoeuver is not found appropriate due to increased safety risk
8. Patients requiring the use of other FSs or PEG-based sealants
9. Patients with any other intra-operative findings identified by the surgeon that may preclude the conduct of the study procedure

4.4 Removal of Patients from Therapy, Assessment, or Study

Any patient may voluntarily withdraw (ie, reduce the degree of participation in the study) consent for continued participation and data collection. The reason for withdrawal will be recorded on the End of Study electronic case report form (eCRF). Assessments to be performed at the termination visit (including in cases of withdrawal or discontinuation) are described in Section 6.16 and Section 7.6.

Discontinuation (ie, complete withdrawal from study participation) may be due to drop out (ie, active discontinuation by patient) or loss to follow-up (ie, discontinuation by patient without notice or action). Additionally, the investigator and the sponsor have the discretion to discontinue any patient from the study if, in their judgment, continued participation would pose an unacceptable risk for the patient.

The data safety monitoring board (DSMB) will upgrade an AE to a serious adverse event (SAE) if the AE results in a patient injury that: jeopardizes the patient and may require medical or surgical intervention, prolongs the hospitalization, requires intervention to prevent permanent impairment or damage, causes disability or permanent damage, causes a congenital anomaly/birth defect, is life-threatening, or results in death.

The study enrolment will be paused and re-evaluated by the DSMB if:

- 2 or more SAEs occur in the same patient and are directly related to the investigational product, across 10 patients, or
- 20 aggregate SAEs occur that are directly related to the investigational product, or
- 1 patient death occurs that is directly related to administration of the investigational product.

The DSMB is required to define the rule(s) appropriate to restart the study, if the above triggering events occur during study conduct.

Discontinuation may also be due to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) or Competent Authority's decision to terminate or suspend approval of the study or the investigator.

5. STUDY TREATMENTS

5.1 Enrolment, Randomisation, and Assignment to a Treatment Group

This is a randomised, single-blind (patient), controlled clinical study. In order to minimize/avoid bias, patients will be randomly assigned to 1 of 2 treatments: IP (FS VH S/D 500 s-apr) OR control (DuraSeal Dural Sealant) with a 1:1 ratio stratified by center and surgical regions (PF or ST).

5.2 Randomisation

Patients will be randomly assigned to FS VH S/D 500 s-apr or DuraSeal Dural Sealant at a ratio of 1:1. Randomisation will be stratified by study center and surgical region (PF or ST) with the goal of achieving an approximate 3:1 ratio (ST:PF) of the 2 surgical regions in the randomised study population. Randomisation will be controlled via an interactive Web-response system (IWRS), [redacted] using dynamic allocation. On the day of surgery (Day 0), upon confirmation of pre-operative eligibility criteria, a member of the site study staff other than the surgeon will obtain a treatment assignment from the IWRS. Adequate amounts of FS VH S/D 500 s-apr and DuraSeal Dural Sealant will be taken into the operating room for potential use as the study treatment.

Immediately after the patient's intra-operative eligibility for study treatment has been confirmed (ie, spontaneous CSF leak or CSF leak after Valsalva manoeuvre), the assigned treatment will be revealed to the surgeon and the assigned IP or control will be applied to the CSF leak site. Following surgery, the treatment assignment and the actual treatment applied will be entered in the eCRF for the patient.

If the patient's eligibility is not confirmed intra-operatively, the operation will be performed according to hospital standards. The study site designee will document the noncompliant criterion or criteria plus the date and reason(s) for the patient's exclusion in the eCRF, and an entry will be made in the IWRS that the study treatment was not administered.

Details of the IWRS and its use will be described in a separate IWRS instruction manual that will be maintained in the trial master file and in each center's investigator trial file.

5.3 Description of Treatments

5.3.1 Investigational Product

FS VH S/D 500 s-apr is to be applied with cannula by dripping in a thin and continuous layer with a 5 mm overlap on each side of the sutured line, ensuring that all suture holes are covered (Appendix 6).

5.3.2 Control

The DuraSeal Dural Sealant is to be applied with the DuraSeal System Applicator by spraying a thin (1 – 2 mm) coating, ensuring that all suture holes are covered (Appendix 7).

5.3.3 Valsalva Manoeuvre

The Valsalva manoeuvre is to be performed by the anaesthesiologist to increase the intra-thoracic pressure (eg, by increasing the positive end-expiratory pressure or by giving a large tidal volume and hold the inflating pressure) to approximately 25 cm H_2O constantly for up to 5 - 10 seconds to transiently elevate the ICP and test for any CSF leaks.

5.3.4 Antibiotic Prophylaxis

All patients, regardless of treatment arm, will have peri-operative antibiotic prophylaxis, according to the guidelines at each site.

5.3.5 Rescue Therapy

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

In case of rescue therapy, the choice of products must be captured in the eCRF (brand name of the material used for rescue therapy, application method, amount used).

5.4 Treatments Administered

Patients who are ≥18 years of age who have signed the ICF and who are eligible by intra-operative inclusion/exclusion criteria will undergo elective cranial surgery with durotomy of the PF or ST region with either craniotomy or craniectomy. The neurosurgical procedures are to be performed according to the standard practices applicable to each indication.

Treatments will be administered intra-operatively, during dural closure, and consist of sutures with FS VH S/D 500 s-apr or sutures with DuraSeal Dural Sealant.

5.4.1 Description of Treatment and Assessment of CSF Leak (Including Valsalva Manoeuvre)

Dura will be closed with sutures, needle sizes, and suturing techniques according to the surgeons' preference. Suture specification must be captured in the eCRF (type, size,

closure technique). Special care will be taken to ensure that if tenting sutures are used, they do not perforate the dura. Use of tenting sutures must be captured in the eCRF.

The surgeon will visually inspect the dural suture line for CSF leakage after application of the allocated treatment (FS VH S/D 500 s-apr or DuraSeal Dural Sealant) and after waiting at least 3 minutes if the treatment is FS VH S/D 500 s-apr. CSF leaks will be defined as any overt flow, seepage, weeping, or sweating of CSF through the dura suture line, regardless of volume. Patients who have a CSF leak, as defined by observing a spontaneous CSF leak or CSF leak after Valsalva manoeuvre (Section 5.3.3) after primary suturing will have their randomisation assignment (Section 5.5) applied.

If the suture line is watertight (ie, no CSF leak), then the suture line must be inspected again after applying the Valsalva manoeuvre (intrathoracic pressure increased to 25 cm H_2O for up to 5 - 10 seconds; Section 5.3.3). If the suture line after the Valsalva manoeuvre is watertight, the treatment is deemed a success, ie, intra-operative CSF leak free.

Note: After the end of the surgical intervention of the brain, physiologic liquids (eg, physiological saline) are to be used to prevent any pneumocephalus and to ensure evaluation of the primary endpoint (no intra-operative CSF leakage and 30 (±3)-day post-operative CSF leakage).

5.5 Method of Assigning Patients to Treatment Groups

The patient will be randomised in a 1:1 allocation ratio stratified by center and surgical regions (PF or ST) to 1 of 2 treatment arms:

- Investigational product: FS VH S/D 500 s-apr

OR

- Control: DuraSeal Dural Sealant

5.6 Blinding

This study will be single-blind (patient), as investigator blinding is not possible due to the visual and physical difference between the 2 treatment regimens. Patients will be kept blinded throughout the study. In addition, the surgeon performing the surgery will remain blinded until intra-operative entry criteria have been confirmed (see Section 5.2).

Otherwise, investigators, surgery personnel, site study personnel, clinical research organisation personnel, and sponsor personnel will not be blinded. Adequate block size will be used to prevent guessing the allocation in the trial and to ensure real blinding. Flexible random block sizes will be also used based on the stratification factors (site and surgical region), eg, relative small block sizes will be used to maintain balance in small strata whereas relative large block sizes will be used in large strata.

5.7 Concomitant Therapy and Prohibited Medications

5.7.1 Concomitant Therapy

The following medications and non-drug therapies are permitted before study entry and during the course of the study:

Medications:

- Prophylactic antibiotics from 1 - 2 days before surgery
- Thrombosis prophylaxis
- Standard use of peri-operative steroids (ie, corticosteroids) is permitted. Chronic steroid use (defined as daily use of corticosteroids for ≥8 weeks) for the purposes of reducing the side effects of chemotherapy and/or radiation therapy for cancer is not exclusionary unless the patient is deemed by the investigator to be suffering from steroid toxicity (ie, Cushing's syndrome) manifested by symptoms and signs such as thin skin, striae, easy bruising, muscle atrophy, upper body obesity, severe fatigue, etc.
- Birth control for women of childbearing potential
- Anesthetic drugs and drugs used in the operating room such as induction agents, volatile anaesthetics, nitrous oxide, narcotics, benzodiazepines, paralytics, cardiovascular drugs, antihypertensives, etc.

Non-drug therapies:

- Concomitant medications and non-drug therapies received from 30 days before enrolment until completion/termination will be recorded on the concomitant medications and non-drug therapies eCRFs.

5.7.2 Prohibited Medications

The following medications and non-drug therapies are **not** permitted before study entry (surgery) and during the course of the study (for the time specified below):

Medications:

- Chemotherapy from 3 weeks prior to, and 7 days after, surgery
- Investigational product from other clinical trials 30 days before and during the entire study or anticipated in the 60-day Follow-up period.

Non-drug therapies:

- Existing CSF drains, Cushing/Dandy cannulation, or Burr holes with damage to the dura before surgery. CSF drains placed during surgery are allowed.
- Use of implants or grafts made of synthetic materials coming into direct contact with dura during surgery
- Placement of Gliadel Wafers during surgery
- Radiation therapy for the head within 7 days following surgery
- Other FSs or PEG-based sealants, unless used as rescue therapy if the assigned study treatment fails

A patient who has taken any of these medications or received any of these non-drug therapies will be excluded according to exclusion criteria (Sections 4.2.2 and 4.3.2). If this occurs after randomisation, it will be regarded as a protocol violation.

5.8 Restrictions

5.8.1 Fluid and Food Intake

No special requirements on fluid and food intake are necessary, other than the standard procedure (ie, no food or liquids after 12 am on the day of surgery).

5.8.2 Patient Activity Restrictions

No special requirements on patient activity are necessary, other than those imposed by the investigator or as per standard post-operative procedure.

5.9 Treatment Compliance

Not applicable.

5.10 Packaging and Labeling

The FS VH S/D 500 s-apr and DuraSeal Dural Sealant batches used in this study will be labeled with the contents, storage instructions, and expiry date, along with other information according to the valid regulatory requirements for clinical trials. The study product is delivered in cardboard boxes.

5.11 Storage and Accountability

The shelf life of FS VH S/D 500 s-apr (frozen) is 24 months, provided that the product is shipped and stored at or below -4°F (-20°C). The cooling chain must be maintained without interruption until application. The unopened product, thawed in an incubator at 98.6°F (37°C), may be stored at 98.6°F (37°C) for up to 4 hours. If the solution is not used within 4 hours after thawing, FS VH S/D 500 s-apr must be discarded. Do not refrigerate or re-freeze. The product must not be used after the expiration date indicated on the label. For additional information on these issues, please see the SmPC.[19]

The shelf life of DuraSeal Dural Sealant is 12 months, provided that the product is shipped and stored below 77°F (25°C). DuraSeal Dural Sealant must be used within 1 hour of preparation.[27]

The investigator will ensure that the IP is stored as specified above and that the storage area is secured, with access limited to authorised study personnel. The investigator will maintain records that the IP was received, including the date received, drug identity code, date of manufacture or expiration date, amount received, and outcome of the product. The IPs must be dispensed only at the study site. Records will be maintained that includes the patient identification code (PIC), dispensation date, and amount dispensed. All remaining partially used and/or unused IP will be destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures for waste of biological human origin. If the IP is to be destroyed, the investigator will provide documentation in accordance with sponsor’s specifications.

6. STUDY PROCEDURES

6.1 Informed Consent

The investigator or designated personnel must explain the study and the implications of participation (e.g., objectives, methods, anticipated benefits, and possible risks) to potential patients according to local regulations prior to any trial related activity. Patients will be informed that their participation is voluntary and that they may withdraw from the study at any time. They will be informed that choosing not to participate or to withdraw from the study will not have an impact on the care the patient will receive for the treatment of his/her disease. In case the patient is unable to read and write, an impartial witness must confirm the informed consent.

The patient will be given sufficient time to read the informed consent form (ICF) and to ask additional questions. After this explanation and before entry in the study, consent should be appropriately recorded by means of the patient's personally dated signature (or, if applicable, by the signature of an independent witness who certifies the patient's consent in writing) and by the investigator's signature. After having obtained the consent, a copy of the signed and dated informed consent must be given to the patient.

Any patient who provides informed consent and meets the general inclusion/exclusion criteria is considered enrolled into the study.

6.2 Demographics

Demographic characteristics to be recorded at pre-operative screening will include age, sex, race, ethnicity, and physical characteristics such as weight and height. Weight will be recorded on Days 0, 5 (±2 days), 30 (±3 days), and 60 (±3 days). Body mass index will be calculated as: BMI = (weight in kilograms / (height in meters x height in meters)).

6.3 Medical History

During pre-operative screening and on Day 0, the patient's medical history will be described for the following body systems including severity or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; haematopoietic/lymphatic; dermatological; and genito-urinary.

6.4 Physical Examination

Physical examination will be performed at pre-operative screening, before and after administration of the study products during surgery (Day 0), at Day 5 (±2 days), at Day 30 (±3 days), at the study completion Day 60 (±3 days), and at any unscheduled

follow-up visit on the following body systems with special attention to the general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, and skin.

During pre-operative screening, if an abnormal condition is detected, the condition will be described on the medical history eCRF. At study visits, if a new abnormal condition or worsened abnormal pre-existing condition is detected, the condition will be described on the AE eCRF. If the abnormal value was not deemed an AE because it was due to an error, due to a pre-existing disease, not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the AE eCRF.

6.5 Neurological Assessment

Neurological assessment will be performed at pre-operative screening, before and after administration of the study products during surgery (Day 0), at Day 5 (±2 days), at Day 30 (±3 days), at the study completion Day 60 (±3 days), and at an unscheduled follow-up visit.

During pre-operative screening, if an abnormal condition is detected, the condition will be described on the medical history eCRF. At study visits, if a new abnormal condition or worsened abnormal pre-existing condition is detected, the condition will be described on the AE eCRF. If the abnormal value was not deemed an AE because it was due to an error, due to a pre-existing disease, not clinically significant, a symptom of a new/worsened condition already recorded as an AE, or due to another issue that will be specified, the investigator will record the justification on the AE eCRF.

6.6 Vital Signs

Vital signs will include body temperature (tympanic; °C), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mm Hg). Blood pressure will be measured when patients are in the supine position.

Vital signs will be measured at pre-operative screening, before and after administration of the study products during surgery (Day 0), at Day 5 (±2 days), at Day 30 (±3 days), at the study completion Day 60 (±3 days), and at any unscheduled follow-up visit.

Vital sign values are to be recorded on the eCRF. For each abnormal vital sign value, the investigator will determine whether or not to report an AE (see definition in Section 6.12 and record the medical diagnosis [preferably], symptom, or sign on the AE eCRF).

Additional tests and other evaluations required to establish the significance or aetiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

6.7 Electrocardiogram

A resting 12-lead electrocardiogram (ECG) will be performed at pre-operative screening and on Days 0, 5 (±2 days), 30 (±3 days), and 60 (±3 days). Patients should be rested for at least 5 minutes in the supine position before the ECG evaluation. Electrocardiograms will be performed before blood sample collection.

Parameters that will be recorded include: heart rate, ventricular polarization (QRS), the interval that extends from the beginning of the P wave (the onset of atrial depolarization) until the beginning of the QRS complex (PR interval), the uncorrected measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle (QT interval), and rhythm analysis.

The pre-operative screening ECG is not necessary if a recent ECG is available as of ≤3 months before planned surgery.

6.8 Clinical Laboratory Tests

6.8.1 Laboratory Parameters

Clinical laboratory parameters will be assessed at pre-operative screening and at Days 0, 5 (±2 days), 30 (±3 days), 60 (±3 days), and any unscheduled follow-up visit (see Appendix 4 for tests and timing). For evaluation of clinical laboratory findings, the investigator will use the Common Terminology Criteria for AEs (CTCAE) toxicity grading scale Version 4.03 as described in Appendix 5.

Women of childbearing potential will be required to take a blood beta-human chorionic gonadotropin (β-hCG) test at pre-operative screening and a urine β-hCG test the day of surgery (Day 0).

Patients will be in a seated or supine position during blood collection. Clinical laboratory tests that will be conducted are presented in Table 1.

Table 1. Clinical Laboratory Tests

Serum Chemistry	Haematology	Coagulation	Spinal Fluid Leak
Alanine aminotransferase (ALT) Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Bilirubin (total and direct) Blood urea nitrogen C-reactive protein Calcium Chloride Creatinine Glucose Glycated haemoglobin (HbA1c) Potassium Sodium Total protein	Haemoglobin Haematocrit Red blood cell (RBC) count Platelet count White blood cell (WBC) count and differential	Prothrombin time Activated partial thromboplastin time (aPTT) International normalised ratio (INR)	Beta-2 (β2)-transferrin (CSF) / Beta-trace protein (CSF)
		Serology	**Pregnancy Test**
		Human immunodeficiency virus (HIV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV), parvovirus B19 (B19V)	Beta-human chorionic gonadotropin (β-hCG) (blood or urine)

6.8.2 Sample Collection, Storage, and Shipping

Blood will be obtained for assessment of haematology and clinical chemistry parameters at pre-operative screening, day of surgery (Day 0), Day 5 (±2 days), Day 30 (±3 days), and at study completion (Day 60 [±3 days]). At study completion, only limited haematology and clinical chemistry parameters will be taken (Appendix 4). Also, if an Unscheduled Follow-up visit occurs between the date of discharge and study completion (Day 60 [±3 days]), haematology and clinical chemistry parameters will be repeated. Haematology and clinical chemistry assessments will be performed at the investigational site. See Appendix 4 for specific details.

6.8.3 Toxicity Grading Scale

Laboratory values will be evaluated according to the CTCAE Version 4.03 toxicity grading scale and captured on the eCRF by the investigator. Grades 3 and 4 will be considered AEs and reported appropriately. The laboratory parameters and the corresponding grading scale are provided in Appendix 5. Laboratory parameters not covered by the CTCAE toxicity scale will be evaluated according to normal values assigned by the local laboratory.

6.8.4 Surgical Site Infections

The surgeon or designated physician will evaluate the patients for SSIs on Follow-up visits at Days 5 (±2 days), 30 (±3 days), and 60 (±3 days), and at unscheduled visits according to the US Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network (NHSN) guidelines found in Appendix 8.

6.9 Dispensing Study Drug

6.9.1 FS VH S/D 500-s

The IP for this protocol is FS VH S/D 500 s-apr in its frozen presentation and must be thawed and prepared using the method described in Appendix 6. When applying FS VH S/D 500 s-apr, the investigator will apply the IP by dripping the FS onto the suture lines. Use of the spray FS formulation (which utilises pressurized gas in the dispensing mechanism) is prohibited during neurosurgery, due to the risk of pneumocephalus, as well as other associated risks, such as air embolism, tissue rupture, or gas entrapment with compression, which may be life-threatening.

Approximately 2 mL FS VH S/D 500 s-apr will be needed to cover a suture line 10 cm long and 1 cm wide (10 cm^2), as per the package insert. Before application, the wound surface should be as dry as possible. Only a thin layer of FS VH S/D 500 s-apr should be applied. Excessive thickness of the fibrin layer may interfere with the product's efficacy and the wound healing process. After application of FS VH S/D 500 s-apr, the IP must rest 3 minutes before the test for CSF leak is evaluated (visual inspection/Valsalva manoeuvre) in order for the IP to polymerize and get sufficient tensile strength.

If needed, a second application of FS VH S/D 500 s-apr is allowed as evaluated by the surgeon; however, avoid re-application of FS VH S/D 500 s-apr to a pre-existing polymerized FS VH S/D 500 s-apr layer because FS VH S/D 500 s-apr may not adhere firmly to a polymerized layer. If a second application of FS VH S/D 500 s-apr is given, it is mandatory to wait for additional 3 minutes before evaluating for CSF leaks (visual

inspection/Valsalva manoeuvre). There is a maximum of 2 allowable applications of the IP.

Important for application of the IP:

- The IP must be warmed to 37°C and maintained at that temperature until ready to apply.
- Keep the dura surface adjacent to the suture as dry as possible immediately before and during application of the IP.
- Expel the first 5 drops from the syringe then begin IP application.
- Apply the IP in a thin layer only.
- In order to provide optimised polymerization, it is important that the IP is not interfered with or manipulated during the resting time of 3 minutes.

If application is interrupted, clogging will occur immediately in the cannula. Replace the application cannula with a new one immediately before application is resumed.

It is important to note that the sealer protein and thrombin solutions are denatured by alcohol, iodine, or heavy metal ions. If any of these substances have been used to clean the wound area, the area must be thoroughly rinsed before application of FS VH S/D 500 s-apr. The wound surface and margins should be as dry and clear of clots, fluids, hemostatic agents, and loose connective tissue as possible Oxidized cellulose-containing preparations may reduce the efficacy of FS VH S/D 500 s-apr and should not be used as carrier materials. Additionally, the safety and efficacy of the combined use of FS VH S/D 500 s-apr with other biocompatible carrier materials has not been evaluated in controlled clinical trials.

6.9.2 DuraSeal Dural Sealant

The control for this protocol, DuraSeal Dural Sealant, must be prepared using the method described in Appendix 7. When applying the DuraSeal hydrogel, the investigator will apply the product by using the DuraSeal Systems applicator to spray the hydrogel onto the suture lines. DuraSeal must be used within 1 hour of preparation.

Before application, the wound surface and margins (2 – 3 mm) around the durotomy edge should be as dry and clear of clots, fluids, hemostatic agents, and loose connective tissue as possible. Only a thin layer (1 – 2 mm) of the DuraSeal hydrogel should be applied. After application of the hydrogel, the patient will be evaluated for CSF leakage (visual

inspection/Valsalva manoeuvre) in order for the product to polymerize and get sufficient tensile strength.

If needed, a second application of the DuraSeal hydrogel is allowed as evaluated by the surgeon; however, avoid re-application of the DuraSeal hydrogel to a pre-existing polymerized DuraSeal because the hydrogel may not adhere firmly to a polymerized layer. If a second application of DuraSeal is given, the patient will be evaluated for CSF leakage (visual inspection/Valsalva manoeuvre). There is a maximum of 2 allowable applications of the control.

If application is interrupted and the spray tip is plugged, remove the spray tip, wipe the applicator tip, and attach a new spray tip and continue delivery. Hydrogel application beyond the edges of the dural margin may be removed with scissors or mechanical disruption. Irrigation immediately after the sealant has solidified is permitted.

6.10 Primary Efficacy Assessments

The primary assessment is defined as the proportion of patients who have neither of the following:

- Intra-operative CSF leakage from dural repair after up to two FS VH S/D 500 s-apr/control applications during Valsalva manoeuvre (25 cm H_2O for up to 5 - 10 seconds)
- Post-operative CSF leakage within 30 (+3) days post-operatively.

Success is defined as: an intra-operative watertight closure of the dura after suturing during surgery after test with the Valsalva manoeuvre (25 cm H_2O for up to 5 - 10 seconds) and no CSF leakage within 30 (+3) days post-operatively.

Failure is defined as: an intra-operative non-watertight closure, which consists of any overt flow, seepage, weeping, or sweating of CSF through the dura suture line, regardless of volume, during surgery or within 30 (+3) days post-operatively.

6.11 Secondary Efficacy Assessments

Secondary efficacy assessments will include:

- Incidence of intra-operative CSF leakage following final Valsalva manoeuvre
- Incidence of CSF leaks within 30 (+3) days post-operatively
- Time in surgery (minutes)

- Time from dural closure (application of IP) until end of surgery
- Length of stay in hospital (days)

All post-operative CSF leaks will be primarily diagnosed based on a detailed history and physical examination including neurological examination. Although not standard of care post-operatively, imaging tests such as computed tomography/magnetic resonance imaging will only be considered if there is a high clinical suspicion of CSF leakage. For example, if CSF leaks externally (eg, incisional leaks, otorrhea, or rhinorrhea), or if there is any bulging suggesting subcutaneous fluid collection at the incision site, needle aspiration and the beta-2 transferrin test or beta-trace protein will be used to confirm the presence of CSF.

6.12 Safety Assessments

The following secondary safety assessments will be performed during this study:

- Incidence of CSF leaks within 60 (+3) days post-operatively
- Incidence of AEs up to 60 (+3) days post-operatively
- Incidence of SSI according to US NHSN within 30 (+3) days post-operatively
- Number of unplanned interventions within 30 (+3) days post-operatively
- Laboratory values and vital signs (e.g., elevated WBC count, fever [temperature >100.7°F or 38.2°C], tachycardia [pulse >100], hypotension [mean arterial pressure <60]).

Adverse events will be evaluated as described in Section 6.13.

Unplanned interventions include the management of meningitis and a deep infection, minimally invasive procedures, the return to the operating room for neurosurgical complications other than a CSF leak or pseudomeningocele formation, or those related to the patient's pre-existing condition during the 30-day follow-up period following original surgical procedure.

Surgical site infections will be evaluated by the surgeon or designated physician according to CDC/NHSN criteria as specified in Appendix 8.

Vital signs and laboratory values will be evaluated as described in Sections 6.6 and 6.8.

6.13 Adverse Events Assessments

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product (IP). (ICH E6 [R2]).

An elective procedure/surgery that occurs during the course of the study (ie, prior to signing the ICF), but is being performed for a documented pre-existing condition and was pre-planned prior to study entry will not qualify as an AE. If, however, there is an increase in the severity, duration, or frequency of a pre-existing disease, the event must be described on the AE eCRF.

An AE can result from the use of the study product or control in accordance with the protocol, as well as from an accidental or intentional misuse of the study product/control or any other treatment error such as unintentional administration or use of another product during the course of the study.

6.13.1 Performing Adverse Events Assessments

During the course of the study, the investigator or designee will routinely monitor and solicit each patient for the occurrence of any AEs, no matter how common they are for a particular patient and regardless of the causality. All AEs (initial, follow-up) will be entered in the eCRF and SAEs (initial, follow-up, upgraded AEs, revisions/amendments) will simultaneously be submitted using a paper SAE Report (SAER) Form.

If a definitive diagnosis has been medically established by the investigator, this diagnosis should then be recorded as the AE. If a definitive diagnosis has not been medically established, the signs and symptoms should then be recorded as the AEs using standard medical terminology, in order to avoid the use of vague, ambiguous, or colloquial expressions.

If a patient experiences an AE, but also additionally a complication of the AE (eg, myocardial infarction with congestive heart failure), both the AE and the additional medical complication should be collected and recorded on CRFs as separate AEs.

Each AE will be evaluated by the investigator for seriousness, severity, and causal relationship to IP/control exposure or study procedure.

For each AE, the outcome (ie, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown) and if applicable action taken (ie, none, drug/device withdrawn, not applicable (AE occurred before drug/device application), or unknown) will also be recorded on the AE eCRF. If the severity rating for an ongoing AE changes before the event resolves, the stop date of this AE will be recorded and a new AE report will be entered with the new severity rating.

Deviations from the protocol-specified dosage (including use of more than the maximum 2 allowable applications of IP/control), treatment errors (including incorrect route of administration, use of an incorrect product, and deviations from the protocol-defined dosing and application schedule), failures of expected pharmacological actions, and unexpected therapeutic or clinical benefits will be followed with regards to occurrence of AEs, lack of efficacy, and/or other observations because these events may be reportable to regulatory authorities.

6.13.2 Timing

In this study, all SAEs and related AEs will be recorded and reported to Baxter Global Pharmacovigilance within 24 hours of awareness beginning at the time the ICF is signed until the event has resolved, stabilized, or returned to baseline or for 30 days after the patient's study completion/termination visit, whichever comes first. If an investigator becomes aware of an SAE occurring in a patient after study completion, the SAE must be reported on the SAER Form within 24 hours after awareness; no additional reporting on eCRFs is necessary.

Adverse events occurring prior to the initiation of the first study procedure will be recorded as signs and symptoms in the patient's medical history. Adverse events occurring between pre-operative screening and the administration of study treatment will be considered as unrelated to study treatment.

For events assessed as not related or unlikely related and occurring within 2 weeks after administration of IP/control, the investigator shall provide the alternative etiology. These causality definitions will also be used to assess the relationship of an AE with a study-related procedure(s), if necessary.

6.13.3 Severity

The investigator will assess the severity of each AE using his/her clinical expertise and judgment based on the most appropriate description below:

- Mild: The AE is a transient discomfort and does not interfere in a significant manner with the patient's normal functioning level and/or the AE resolves spontaneously or may require minimal therapeutic intervention.
- Moderate: The AE produces limited impairment of function and may require therapeutic intervention and/or the AE produces no sequela/sequelae.
- Severe: The AE results in a marked impairment of function and may lead to temporary inability to resume usual life pattern and/or the AE produces sequela/sequelae, which require (prolonged) therapeutic intervention.

These severity definitions will also be used to assess the severity of an AE with a study-related procedure(s), if necessary.

6.13.4 Relationship

Causality is a determination of whether there is a reasonable possibility that the IP/control is etiologically related to/associated with the AE. Causality assessment includes, assessment of temporal relationships, de-challenge/re-challenge information, association (or lack of association) with underlying disease, presence (or absence) of a more likely cause, and physiological plausibility. For each AE, the investigator will assess the causal relationship between the IP/control and the AE using his/her clinical expertise and judgment according to the following most appropriate algorithm for the circumstances of the AE:

- Not related (both circumstances must be met).
    1. Is due to underlying or concurrent illness, complications, concurrent treatments, or effects of concurrent drugs.
    2. Is not associated with the IP/control (ie, does not follow a reasonable temporal relationship to the administration of IP/control or has a much more likely alternative aetiology).
- Unlikely related (either 1 or both circumstances are met).
    a. Has little or no temporal relationship to the IP/control.
    b. A more likely alternative aetiology exists.
- Possibly related (both circumstances must be met).
    a. Follows a reasonable temporal relationship to the administration of IP/control.

b. An alternative aetiology is equally or less likely compared to the potential relationship to the IP/control.

- Probably related (both circumstances must be met).
  a. Follows a strong temporal relationship to the administration of IP/control, which may include but is not limited to the following:
     a. Reappearance of a similar reaction upon re-administration (positive re-challenge).
     b. Positive results in a drug sensitivity test (skin test, etc.).
     c. Toxic level of the IP/control as evidenced by measurement of the IP/control concentrations in the blood or other bodily fluid.
  b. Another aetiology is unlikely or significantly less likely.

6.13.5 Expectedness

The only expected AEs that may be related to the IP/control in this study is the reaction to the IP/control (i.e., allergic reaction), which will be evaluated and if observed, standard-of-care will be applied. Patients with an aprotinin allergy will be excluded from the study.

A suspected unexpected serious adverse reaction is any adverse reaction that is classified as serious and is suspected to be caused by the investigational drug but is not consistent with the information found in the product current IB. For the purposes of this study, each unexpected AE experienced by a patient undergoing neurosurgical intervention will be recorded on the AE eCRF.

6.13.6 Adverse Events of Special Interest

Patients will be closely monitored for any signs of sterile meningitis during surgery and follow-up visits. In case signs and symptoms of sterile meningitis are present during the study, the investigator will assess these symptoms, and order and review diagnostic procedures, as appropriate, to confirm the diagnosis.

6.13.7 Clinical Laboratory Adverse Events

The investigator's assessment of each relevant laboratory value will be recorded on the eCRF. For each abnormal laboratory value, the investigator will determine whether the value is considered clinically significant or not. For clinically significant values, the investigator will indicate if the values constitute a new AE and record the sign, symptom, or medical diagnosis on the AE eCRF. The investigator will also record on the AE eCRF

whether the clinically significant values are symptoms or related to previously recorded AEs, are due to pre-existing diseases, or are due to other issues. Adverse events that are grade 3 and 4 will be considered AEs and reported appropriately. The laboratory parameters and the corresponding grading scale are provided in Appendix 4. Additional tests and other evaluations required to establish the significance or aetiology of an abnormal value or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

Any seroconversion result for HIV, HAV, HBV, HCV, hepatitis E virus (HEV), or parvovirus B19 (B19V) shall be re-tested.

6.13.8 Serious Adverse Events

6.13.8.1 Definition

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes: death, life-threatening AE, hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Moreover, reviewed and confirmed seroconversion for HIV, HAV, HBV, HCV, HEV, or B19V will also be important medical events that shall qualify as an SAE.

6.13.8.2 Reporting Serious Adverse Events

The investigator will report all SAEs to the pharmacovigilance safety desk of the contract research organisation (CRO). The CRO will verify that the applicable laws/requirements for reporting SAEs to the Institutional Review Boards (IRBs)/Ethics Committees (ECs) are followed by the sponsor (Baxter). The sponsor will expedite the SAER forms to the appropriate regulatory authority(ies).

- ALL SAEs ARE TO BE REPORTED TO THE CRO'S SAFETY DESK ON THE SAER FORM WITHIN 24 HOURS AND TRANSMITTED ALONG WITH ANY DE-IDENTIFIED SUPPORTING DOCUMENTATION IN THE ENGLISH LANGUAGE TO THE SPONSOR WITHIN 24 HOURS OF BECOMING AWARE OF THE EVENT

See SAER form for contact information. **Further details are also available in the study team roster.**

For definitions and information on the assessment of these events, refer to the following:

- Section 6.13, Adverse Events Assessments
- Section 6.13.1, Performing Adverse Events Assessments
- Section 6.13.8, Serious Adverse Events

6.13.9 Urgent Safety Measures

An urgent safety measure is an immediate action taken, which is not defined by the protocol, in order to protect patients participating in a clinical trial from immediate harm. Urgent safety measures may be taken by the sponsor or clinical investigator, and may include any of the following:

- Immediate change in study design or study procedures
- Temporary or permanent halt of a given clinical trial or trials
- Any other immediate action taken in order to protect clinical trial participants from immediate hazard to their health and safety.

The investigator may take appropriate urgent safety measures in order to protect patients against any immediate hazard to their health or safety. The measures should be taken immediately and may be taken without prior authorisation from the sponsor. In the event(s) of an apparent immediate hazard to the patient, the investigator will notify the sponsor immediately by phone and confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The investigator will also ensure the responsible IRB/EC and national competent authority (NCA) is notified of the urgent measures taken in such cases according to local regulations. The CRO should verify that the responsible IRB/EC and the sponsor (Baxter) have been informed of the event in an expedited manner as stated above.

6.13.10 Untoward Medical Occurrences

Untoward medical occurrences occurring before the first exposure to IP/control are not considered AEs; however, each serious untoward medical occurrence experienced before the first IP/control exposure (ie, from the time of signed ICF up to but not including the first IP/control exposure) will be described on the SAER form.

6.13.11 Treatment-emergent Adverse Events

A treatment-emergent AE is defined as any AE that occurs after the onset of study treatment administration through the end of the study.

6.14 Concomitant Medication Assessments

Ongoing prior medications will be recorded as concomitant medication once the study treatment has been initiated. During treatment, concomitant medications and therapies (including dose, frequency, start and stop dates, and indication for use), will be recorded in the eCRF by study site personnel on a daily basis.

6.15 Non-Medical Complaints

A non-medical complaint (NMC) is any alleged product deficiency that relates to identity, quality, durability, reliability, safety, and performance of the product but does not result in an AE. Non-medical complaints include but are not limited to the following:

- A failure of a product to exhibit its expected pharmacological activity and/or design function (eg, reconstitution difficulty).
- Missing components.
- Damage to the product or unit carton.
- A mislabelled product (eg, potential counterfeiting/tampering).
- A bacteriological, chemical, or physical change or deterioration of the product causing it to malfunction or to present a hazard or fail to meet label claims.

Any NMCs of the product will be documented on an NMC form and reported to the sponsor within 1 business day. If requested, the defective product(s) will be returned to the sponsor for inspection and analysis according to procedures.

6.16 Removal of Patients from the Trial or Study Drug

A patient is considered to have completed the study when he/she ceases active participation in the study because the patient has, or is presumed to have, completed all

study procedures according with the protocol (with or without protocol deviations). Any other cases are classified as discontinuation.

Reasons for completion/discontinuation will be reported on the Completion/Discontinuation eCRF, including: Completed, AE (eg, death), discontinuation by patient (eg, lost to follow-up [defined as 3 documented unsuccessful attempts to contact the patient], dropout), physician decision (eg, pregnancy, progressive disease, protocol violation[s], recovery), study terminated by sponsor, or other (reason to be specified by the investigator [eg, technical problems]). Screening failures will be recorded on the Screening Failures form. Regardless of the reason, all data available for the patient up to the time of completion/discontinuation should be recorded on the appropriate eCRF.

Every effort will be made to have discontinued patients complete the study completion/termination visit. If the completion/termination visit is done as an additional, unscheduled visit, the assessment results shall be recorded with the completion/termination visit. If a patient terminates participation in the study and does not return for the completion/termination visit, his/her last recorded assessments shall remain recorded with his/her last visit. The reason for discontinuation will be recorded and the data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report. If additional assessments are required, the assessments shall be recorded separately. Assessments to be performed at the termination visit (including cases of withdraw or discontinuation) can be found in Appendix 2 (Schedule of Study Procedures and Assessments) and Appendix 4 (Clinical Laboratory Assessments).

In the event of patient discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the investigator in consultation with the sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the sponsor.

6.17 Appropriateness of Measurements

Measurements to be performed during the course of the study (with the following exceptions) are standard for the indication or patient population under study:

- The Valsalva manoeuvre, while not standard, is necessary to assess intra-operative CSF leakage that may not be easily identified on visual inspection.

7. STUDY ACTIVITIES

7.1 Screening and Study Visits

The study site is responsible for maintaining an enrolment/screening log that includes all patients enrolled. The log will also serve to document the reason for screening failure.

The overall study design is illustrated in Appendix 1. Details on the procedures to be performed at each study visit, including screening, can be found in Appendix 2 (Schedule of Study Procedures and Assessments) and Appendix 4 (Clinical Laboratory Assessments).

7.2 Pre-operative Screening Visit (Days -30 to -1)

- Obtain IC.
- During the pre-operative screening visit, the investigator will determine if the patient meets all pre-operative inclusion criteria and none of the pre-operative exclusion criteria.
- Record demographics (including weight, height, and body mass index), medical history, physical examination results, an assessment of neurological status, vital signs, and ECG results.
- Measure baseline clinical laboratory values (see Appendix 4).
- Record AEs.
- Record concomitant medications and non-drug therapies.

7.3 Procedures for Day 0 Treatment (Pre-operative)

- Re-assess patient to confirm that the patient is ready for surgery and meets the pre-operative inclusion criteria and none of the exclusion criteria. No changes in health status have occurred between the initial screening and the day of surgery that would affect the patient and/or study conduct.
- Record medical history, physical examination results, an assessment of neurological status, vital signs, and weight.
- Perform a urine screening for pregnancy test (for women of childbearing potential). If screening occurred more than 48 hours prior to performing the operation, baseline clinical laboratory values (see Appendix 4) will be measured.
- Record AEs.

- Record concomitant medications and non-drug therapies.
- Perform pre-operative randomisation (surgeon remains blinded to treatment until intra-operative screening is complete, as described in Section 7.4)

7.4 Procedures for Day 0 Treatment (During and After Surgery)

- Perform intra-operative screening for inclusion and exclusion criteria and a check for CSF leak after placing primary suture.
- Randomised treatment is revealed to the surgeon
- Apply IP or control treatment to the CSF leak site.
- Administer peri-operative antibiotic.
- Collect the following surgery details:
  - Start (skin cut),
  - Start (application of IP/control),
  - End (last skin suture),
  - Length of sutured durotomy (cm),
  - Surgical complications,
  - Suture type used for dura closure (brand, type, size),
  - Suture closure technique (eg, continuous simple, continuous locked, interrupted),
  - Use of autologous or non-autologous dural material,
  - Use of tenting sutures (Yes/No),
  - Rescue therapy (Yes/No, if Yes: reason, brand, type, technique).
- Assess primary endpoint part 1: check for CSF leakage (Yes/No) after up to two IP/control applications during the Valsalva manoeuver (up to 25 cm H_2O for up to 5 - 10 seconds). Any visible CSF is considered positive for CSF leak.
- Post-operatively, monitor vital signs and perform physical examination, neurological assessment, and ECG.

7.5 Procedures for Day 5 (±2 Days) or the Day Before Discharge (Whichever Comes First), and Day 30 (±3 Days)

- Record physical examination results, an assessment of neurological status, vital signs, ECG, and weight.
- Measure clinical laboratory values (see Appendix 4).
- Assess primary endpoint part 2: check for CSF leakage.
- Assess surgical site.
- Document any need for surgical revision.
- Check drain duration and output, if present.
- Document the number of unplanned interventions.
- Record AEs.
- Record concomitant medications and non-drug therapies.

7.6 Procedures for Day 60 (±3 Days) and/or Study Completion

- Record physical examination results, an assessment of neurological status, vital signs, ECG, and weight.
- Measure clinical laboratory values (see Appendix 4).
- Perform assessment of CSF leak.
- Assess surgical site.
- Document any need for surgical revision.
- Document length of stay and number of days in the intensive care unit (ICU).
- Document the number of unplanned interventions.
- Record AEs.
- Record concomitant medications and non-drug therapies.

7.7 Procedures for Unscheduled Follow-up (Between Days 5 [±2] to 60 [±3])

- Record physical examination results, an assessment of neurological status, and vital signs.
- Measure clinical laboratory values (see Appendix 4).
- Perform assessment of CSF leak.
- Assess surgical site.

- Document any need for surgical revision.
- Record AEs.
- Record concomitant medications and non-drug therapies.

8. QUALITY CONTROL AND ASSURANCE

8.1 Auditing

The sponsor and/or sponsor's representatives may conduct audits to evaluate study conduct and compliance with the protocol, standard operating procedures, other written instructions/agreements, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), the IRB/IEC and applicable regulatory guidelines/requirements. The investigator will permit auditors to visit the study site, as described in the Clinical Study Agreement. Auditing processes specific to the study will be described in the auditing plan.

8.2 Non-compliance with the Protocol

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the patient. In the event(s) of an apparent immediate hazard to the patient, the investigator will notify the CRO immediately by phone and will confirm notification to the CRO in writing as soon as possible, but within 1 calendar day after the change is implemented. The investigator will also ensure the responsible IRB/EC/NCA is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the CRO may terminate the investigator's participation. The CRO will notify the IRB/EC and applicable regulatory authorities of any investigator termination.

9. PLANNED STATISTICAL METHODS

9.1 General Considerations

The Statistical Analysis Plan (SAP) is a separate document that will provide a more technical and detailed elaboration of the principal features stated in the protocol. Any deviations from the planned analyses will be described and justified in the final clinical trial report.

9.2 Determination of Sample Size

This study is designed to show non-inferiority (NI) of FS VH S/D 500 s-apr compared to DuraSeal Dural Sealant based on the primary composite efficacy endpoint. The proportion of patients meeting the composite primary endpoint is assumed to be [redacted]% for FS VH S/D 500 s-apr and [redacted]% for DuraSeal. Using a non-inferiority margin of 10% (the largest clinically acceptable difference), a 1-sided Type 1 error rate (α) of 2.5%, a statistical power (1-β) of 80%, that one interim analysis is performed after 50% of the patients complete the study, the sample size estimation results in 202 evaluable patients. Assuming a group sequential design utilising O'Brien-Fleming boundaries, the study may be stopped early for futility if a p-value >0.2486 is observed at the interim. The estimation of sample size was performed using [redacted] software ([redacted], [redacted]).

The primary analysis will be performed on the per protocol set (PPS). Assuming that the PPS is 10% less than the total number of randomised patients, 112 patients per treatment group should be randomised, and there will be 224 patients in total.

9.2.1 Justification of Non-Inferiority Margin

The 10% NI margin is mainly based on literature review, the screening of multiple key opinion leaders (clinical judgment), and a previous clinical study for a comparable product that led to biologic license application (BLA) approval.

- Literature review (Weber 2012)[8]: In a retrospective analysis of 1395 cranial surgeries, post-operative CSF leaks occur in approximately 7.7%, across all types of cranial surgeries. However, tight dural sutures by inspection were followed by CSF leaks in 4.7%. Tight suturing of the dura mater with additional securing and/ or augmentation of the suture by a different technique (covering with muscle or fascia flab, gelitta, fibrin glue, hydrogel gel, or others) is performed 68% of the time. The subgroups with different dural closure augmentation techniques

(fleece-bound sealant, glue, dural-plasties, etc.) were too small to detect any statistically demonstrable effect on CSF leaks after cranial surgery.

- Clinical judgment: Based upon discussion with clinicians (neurosurgeons) on the use of dural sealants as an adjunct to suture line, the consensus was that NI could be claimed if the maximum difference of success rate (ie, CSF leakage free) between the new treatment (Tisseel) and the current treatment (DuraSeal) is 10%, with the assumption that the proportion of patients meeting the composite primary endpoint is at least 85.0% for DuraSeal.
- Previous clinical study: A 10% NI margin was used in a previous Phase III pivotal, NI study. In this study, a new dural sealant (Adherus) was compared to the same control (DuraSeal) and the study design including patient population, eligibility criteria, and the primary endpoint was very similar to the current Tisseel study.[29] Thus, the assumed proportion of 90.6% for DuraSeal in the current Tisseel study is based on results of this previous study evaluating Adherus and DuraSeal.

9.3 Analysis Populations

9.3.1 Full Analysis Set (FAS)

The patients who were randomised and treated with at least 1 dose of IP/control will be included in the Full Analysis Set (FAS).

9.3.2 Per Protocol Set (PPS)

The patients included in the FAS without any major protocol deviations, which could impact the primary endpoint assessment, will be included in the Per Protocol Set (PPS). The PPS is defined by the following:

- Patients who meet all inclusion criteria and do not meet any exclusion criteria.
- Patients who are randomised and treated according to the randomisation scheme.
- Patients with no major protocol deviations which could impact the primary endpoint assessment.
- Availability of primary endpoint assessment.

Furthermore, any other major protocol violations, such as serious unforeseen violations deemed to invalidate the data and affect the conclusions of the study, will lead to the exclusion of patients from the PPS.

9.3.3 Safety Analysis Set

The patients who received at least 1 dose of IP/control will be included in the Safety Analysis Set. Patients will be analysed as treated (in case of incorrect randomisations).

9.4 Methods of Analysis

The efficacy endpoints will be analysed for the FAS and the PPS, with the PPS being considered as primary and the FAS as supportive.

The safety endpoints will be analysed for the safety data using the safety analysis set.

Categorical data will be summarised using frequencies and percentages, while continuous data will be presented using descriptive summary statistics (the number of patients [N], mean, standard deviation, median, minimum, and maximum).

No imputation of missing data will be performed, unless otherwise specified.

All efficacy and safety endpoints will be listed in patient data listings.

9.4.1 Demographics and Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for the FAS population by treatment group and total in order to assess the degree of similarity achieved.

9.4.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients who have neither of the following:

- Intra-operative CSF leakage from dural repair after up to two FS VH S/D 500 s-apr/control applications during Valsalva manoeuver (25 cm H_2O for up to 5 - 10 seconds)
- Post-operative CSF leakage within 30 (+3) days post-operatively

The specific hypotheses of the proportion difference to be tested are as follows:

H_0: $P_{FS} - P_{DS} \leq -0.10$

H_a: $P_{FS} - P_{DS} > -0.10$

where

P_{FS} = the proportion of patients not meeting the 2 criteria (ie, no intra-operative CSF leakage and no post-operative CSF leakage) for the FS VH S/D 500 s-apr treatment group, and

P_{DS} = the proportion of patients not meeting the 2 criteria (ie, no intra-operative CSF leakage and no post-operative CSF leakage) for the DuraSeal Dural Sealant treatment group.

The primary composite efficacy endpoint, proportion of patients not meeting the 2 criteria (ie, no intra-operative CSF leakage and no post-operative CSF leakage), will be investigated by a 2-sided test for non-inferiority using logistic regression, taking into account the following covariates: study center and surgery region. Non-inferiority of FS VH S/D 500 s-apr to DuraSeal Dural Sealant will be assessed using the confidence interval approach and a NI margin of 10%.

9.4.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints are the following:

- Incidence of intra-operative CSF leakage following final Valsalva manoeuver
- Incidence of CSF leaks within 30 (+3) days post-operatively
- Time in surgery (minutes)
- Time from dural closure (application of IP) until end of surgery
- Length of stay in hospital (days)

The logistic regression approach used for the primary efficacy endpoint will also be used to calculate the proportions of patients with incidence of intra-operative CSF leakage following final Valsalva manoeuver and incidence of CSF leaks within 30 (+3) days post-operatively.

The time in surgery, time from dural closure until end of surgery, and the length of stay in hospital will be compared between the 2 groups using a Wilcoxon rank sum test.

9.4.4 Secondary Safety Endpoints

The secondary safety endpoints are the following:

- Incidence of CSF leaks within 60 (+3) days post-operatively
- Incidence of AEs up to 60 (+3) days post-operatively
- Incidence of SSIs according to US NHSN within 30 (+3) days post-operatively
- Number of unplanned interventions within 30 (+3) days post-operatively
- Laboratory values and vital signs (e.g., elevated WBC count, fever [temperature >100.7°F or 38.2°C], tachycardia [pulse >100], hypotension [mean arterial pressure <60]).

The logistic regression approach used for the primary efficacy endpoint will be used to calculate the proportions of patients with: incidence of CSF leaks within 60 (+3) days post-operatively, and incidence of SSIs according to NHSN within 30 (+3) days post-operatively. The duration and incidence of each laboratory and vital sign abnormality will be recorded. Abnormal laboratory values will be observed, followed, and managed by the investigator for a return to baseline, per standard of care.

The number of unplanned interventions within 30 (+3) days post-operatively will be compared between the 2 treatment groups using a Wilcoxon rank sum test.

An AE overview summary table will be prepared including the number of patients reporting an AE, the percentage of patients (%) with an AE, and the number of events reported, for the following categories:

1. Deaths.
2. SAEs.
3. AEs leading to withdrawal.
4. Severe AEs.
5. Related AEs.
6. AEs of special interest.

Adverse events will be tabulated by body system using the Medical Dictionary for Regulatory Activities (MedDRA). The table will display the total number of patients reporting an AE, the percentage of patients (%) with an AE, and the number of events

reported by system organ class (SOC) and preferred term. In addition, tables will be summarised by SOC, preferred term, and severity.

These tables will be produced for:

- All AEs.
- AEs with an incidence ≥5% of patients in any treatment arm.
- Non-serious AEs with an incidence ≥5% of patients in any treatment arm.
- AEs by causality (related/unrelated).
- AEs leading to death.
- AEs by severity.
- SAEs.
- AEs leading to withdrawal.

Listings will be prepared for:

- All AEs sorted by center and patient.
- SAEs.
- AEs leading to death.
- AEs leading to withdrawal.
- Laboratory results and vital signs.

9.5 Interim Analysis

An interim analysis will be conducted after the completion of 50% of patients. A group sequential design utilising O'Brien-Fleming boundaries will be carried out. Basic demographic tables will be produced during the interim analysis. The study may be stopped early for futility if a p-value >0.2486 is observed. If the study is stopped early, a full analysis of all of the data will be produced.

10. ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

The investigator will comply with the protocol (which has been approved/given favourable opinion by the IRB/EC/NCA), ICH GCP, the ethical principles of the Declaration of Helsinki, and applicable regulatory requirements as described in the Clinical Study Agreement. The investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the sponsor. Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site. Sub-investigators or other authorised study personnel are eligible to sign for the investigator, except where the investigator's signature is specifically required.

10.2 Institutional Review Board (IRB) or Ethics Committee (EC) Approval

Before the enrolment of patients into this study, the protocol, ICF, any promotional material/advertisements, and any other written information to be provided will be reviewed and approved/given favourable opinion by the IRB/EC and applicable regulatory authorities. The IB will be provided for review and/or approval by the IRB/EC, if required. The IRB/EC's composition will be documented and filed in to the respective investigator's study file. The study will commence only upon the sponsor's receipt of approval/favourable opinion from the IRB/EC and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval, as described in the Clinical Study Agreement.

If the protocol, any other information given to the patient or any other study documents (eg, IB, Investigational Medicinal Product Dossier) is substantially amended, the revised documents will be reviewed and approved/given favourable opinion by the IRB/EC and applicable regulatory authorities, where applicable. Any substantial protocol amendment will only be implemented upon the sponsor's receipt of approval and, if required, upon the sponsor's notification of applicable regulatory authority(ies) approval.

10.3 Ethical Conduct of the Study

This study will be conducted in accordance with the following guidelines:

- Declaration of Helsinki (current version).
- Current ICH Guidelines (ICH E6) for GCP Guidelines.
- Basic principles defined in US 21 Code of Federal Regulations Part 312.

- IRBs/IECs requirements.
- All local legal requirements of the countries, where the study is being conducted.

10.4 Patient Information and Consent

Investigators will choose patients for enrolment considering the study eligibility criteria. The investigator will exercise no selectivity so that no bias is introduced from this source.

All patients must personally sign and date an ICF before entering into the study according to applicable regulatory requirements and ICH GCP. Before use, the ICF will be reviewed by the sponsor and approved by the IRB/EC and regulatory authority(ies), where applicable. The ICF will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable regulatory requirements. Patients will be allowed sufficient time to consider participation in the study. By signing the ICF, patients agree that they will complete all evaluations required by the study, unless they withdraw voluntarily or are terminated from the study for any reason.

The sponsor will provide to the investigator, in written form, any new information that significantly bears on the patients' risks associated with IP exposure. The IC will be updated, if necessary. This new information and/or revised ICF, which have been approved by the applicable IRB/EC and regulatory authorities, where applicable, will be provided by the investigator to the patients who consented to participate in the study.

10.5 Patient Confidentiality

The investigator will comply with applicable patient privacy regulations/guidance as described in the Clinical Study Agreement.

10.6 Training

The study monitor will ensure that the investigator and study site personnel understand all requirements of the protocol, the investigational status of the IP, and his/her regulatory responsibilities as an investigator. Training may be provided at an investigator's meeting by Baxter staff, at the study site, and/or by instruction manuals. In addition, the study monitor will be available for consultation with the investigator and will serve as the liaison between the study site and the sponsor. A Baxter representative may be present for the first surgery for each site.

10.7 Insurance

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the clinical study. For patients treated according to the clinical study protocol, injury possibly arising from participating in this study is covered by the liability insurance of the sponsor, unless malpractice from the investigator.

10.8 Study Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

a. Data are authentic, accurate, and complete.
b. Supporting data may be requested.
c. Safety and rights of patients are being protected.
d. Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol).

Any other study agreements, ICH GCP, IRBs/IECs, and all applicable regulatory requirements are met. The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

10.9 Electronic Case Report Forms and Study Records

Study documentation may include information defined as "source data", records detailing the progress of the study for each patient, signed ICFs, correspondence with the IRB/EC and the study monitor/sponsor, enrolment and screening information, eCRFs, SAER forms, laboratory reports (if applicable), and queries.

The investigator will comply with the procedures for data recording and reporting.

The investigator is responsible for the procurement of data and for the quality of data recorded on the eCRFs. The case report forms will be provided in electronic form.

Electronic case report forms will be provided by the sponsor/designee, only authorised study site personnel will record or change data on the eCRFs. Changes to an eCRF will

require documentation of the reason for each change in the source documents. An identical (electronic/paper) version of the complete set of eCRFs for each patient will remain in the investigator file at the study site in accordance with the data retention policy and contractual obligations.

The handling of data by the sponsor, including data quality assurance, will comply with regulatory guidelines (eg, ICH GCP and local legal requirements) and the standard operating procedures of the sponsor. Data management and control processes specific to the study will be described in the data management plan.

10.10 Data Safety Monitoring Board

This study will be monitored by an independent unblinded DSMB. The DSMB will be composed of 3 members, 2 members who are recognized experts in the field of neurosurgery clinical care and research and 1 member who is a biostatistician. One (1) of the members shall serve as chairperson of the DSMB. The DSMB neurosurgeons will not be involved in enrolling or treating study patients.

The DSMB will monitor ongoing safety data (AEs and laboratory test results). The DSMB will review safety and efficacy data from the study after 50% of the patients have been completed, and will have the discretion to recommend stopping the trial due to safety, efficacy, or futility concerns. The rules to pause the study enrolment and re-evaluate the study are presented in Section 4.4.

10.11 Protocol Violations/Deviations

The investigator may deviate from the protocol only to eliminate an apparent immediate hazard to the patient. In the event(s) of an apparent immediate hazard to the patient, the investigator will notify the sponsor immediately by phone and will confirm notification to the sponsor in writing as soon as possible, but within 1 calendar day after the change is implemented. The investigator will also ensure the responsible IRB/EC and the responsible NCA, if applicable, is notified of the urgent measures taken in such cases according to local regulations.

If monitoring and/or auditing identify serious and/or persistent non-compliance with the protocol, the sponsor may terminate the investigator's participation. The sponsor will notify the IRB/EC and applicable regulatory authorities of any investigator termination.

10.12 Auditing

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess

the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome. In addition, inspections by regulatory health authority representatives and IRB(s)/EC(s) are possible. The investigator should notify the sponsor immediately of any such inspection. The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

10.13 Access to Source Documentation

Per ICH GCP, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format. Source data for this study comprise the hospital records, medical records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, outcomes reported by patients, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study.

The investigator/study site will cooperate and provide direct access to study documents and data, including source documentation for monitoring by the study monitor, audits by the sponsor or sponsor's representatives, review by the IRB/EC, and inspections by applicable regulatory authorities, as described in the Clinical Study Agreement. If contacted by an applicable regulatory authority, the investigator will notify the sponsor of contact, cooperate with the authority, provide the sponsor with copies of all documents received from the authority, and allow the sponsor to comment on any responses, as described in the Clinical Study Agreement.

10.14 Data Generation and Analysis

The study data will be entered into a validated, audit-trailed, Part 11 compliant Electronic Data Capture system. Computerised data checks will be used to supplement manual review to check for data omissions, inconsistencies, and out of range values.

10.15 Retention of Data

The investigator will retain study documentation and data (paper and electronic forms) in accordance with applicable regulatory requirements and the document and data retention policy, as described in the Clinical Study Agreement.

10.16 Financial Disclosure

The investigator will comply with investigator financing, investigator/sponsor insurance, and patient compensation policies, if applicable, as described in the Clinical Study Agreement.

10.17 Publication and Disclosure Policy

The investigator will comply with the publication policy as described in the Clinical Study Agreement.

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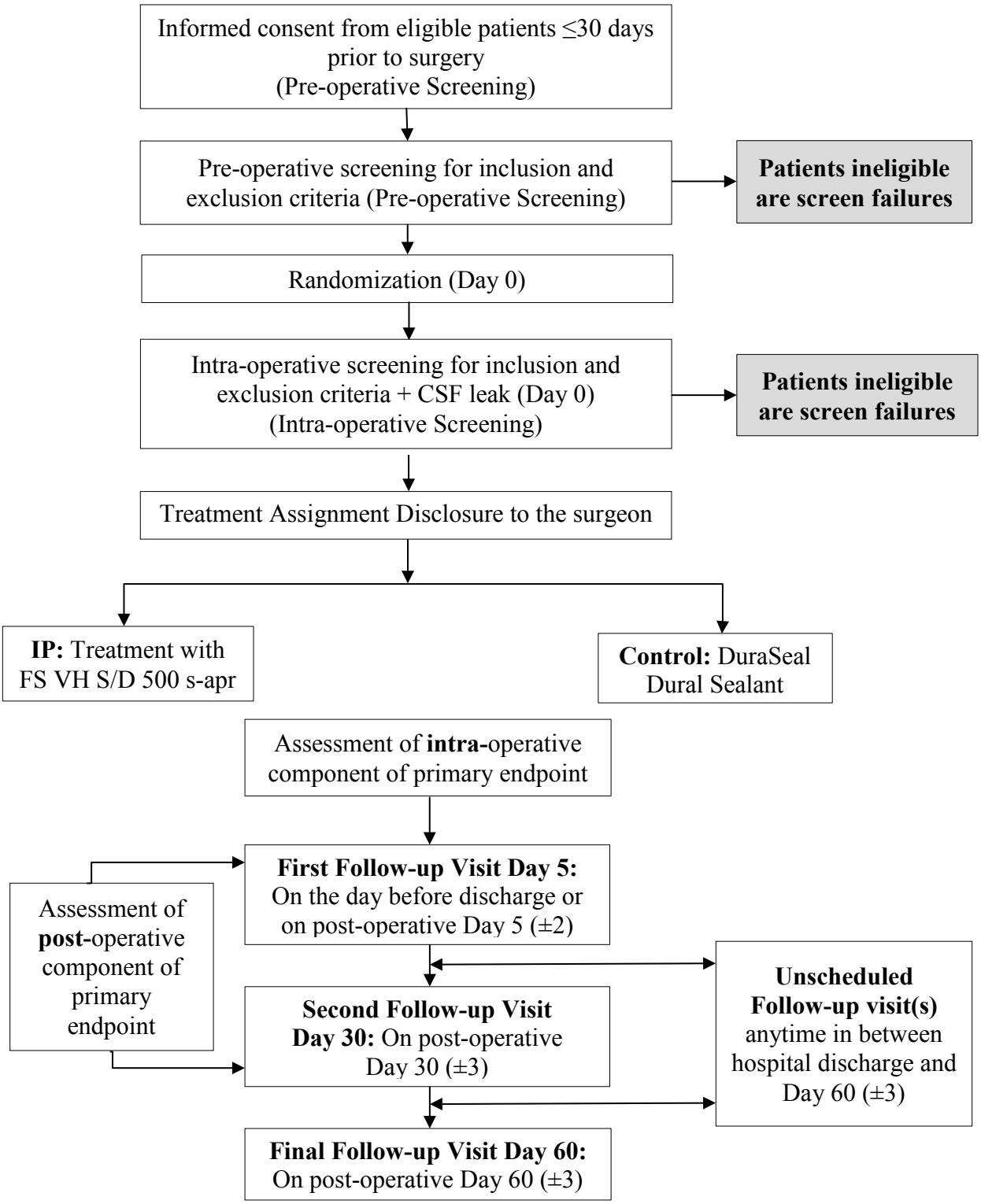
Appendix 1 Study Design with Study Visits (Screening, Days 0, 5, 30, and 60)



Appendix 2 Schedule of Procedures and Assessments

Procedures and Assessments	Pre-operative Screening Visit (Day -30 to -1)	Surgery Day 0	Post-operative Study Visits			
			Day 5 (±2 days) or Day Before Discharge, Whichever Comes First	Day 30 (±3 days)	Study Completion[a] Day 60 (±3 days)	Unscheduled Follow-up (Between Days 5 [±2] - 60 [±3])
Informed consent[b]	X					
Eligibility criteria	X	X				
Demographics[c]	X	X	X	X	X	
Medical history	X	X				
Medications	X	X	X	X	X	X
Non-drug therapies	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X
Assessment of neurological status	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Laboratory tests[d]	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
12-lead ECG	X[e]	X	X	X	X	
IP treatment[f]		X				
Antibiotic prophylaxis		X				
Randomisation		X				
Surgery details[g]		X				
Assessment of CSF leak		X	X	X	X	X

Procedures and Assessments	Pre-operative Screening Visit (Day -30 to -1)	Surgery Day 0	Post-operative Study Visits			
			Day 5 (±2 days) or Day Before Discharge, Whichever Comes First	Day 30 (±3 days)	Study Completion[a] Day 60 (±3 days)	Unscheduled Follow-up (Between Days 5 [±2] - 60 [±3])
Valsalva manoeuver[h]		X				
Assessment of surgical site			X	X	X	X
Length of stay[i]					X	
Documentation on need for surgical revision[j]			X	X	X	X
Days in ICU					X	
Drain duration and output			X	X		
Document the number of unplanned interventions			X	X	X	

CSF=cerebrospinal fluid; ECG=electrocardiogram; ICU=intensive care unit; IP=investigational product; SSI=surgical site infection.

[a] Includes cases of withdrawal or discontinuation.

[b] Occurs at enrolment (prior to any study specific procedure).

[c] On Days 0, 5 (±2), 30 (±3), and 60 (±3), weight will also be recorded. On the pre-operative screening visit (Day -30 to -1), height will be recorded and body mass index will be calculated.

[d] For laboratory assessments, see Appendix 4.

[e] Not necessary if a recent ECG is available as of ≤3 months before planned surgery.

[f] IP product details to be captured: amount of product used (mL), number of applications (1 or 2), problems occurring during application.

[g] Surgery details to be captured: start (skin cut), start (application of IP/control),end (last skin suture), length of sutured durotomy (cm), surgical complications, suture type used for dura closure (brand, type, size), suture closure technique (continuous simple, continuous locked, interrupted), use of autologous or non-autologus dural material), use of tenting sutures (Y/N), rescue therapy (Y/N, brand, type, technique).

[h] CSF leakage will be assessed after up to two IP/control applications during the Valsalva manoeuver (up to 25 cm H_2O for up to 5 – 10 seconds).

[i] Days in hospital (Day 0 - Discharge).

[j] Re-do surgery details to include: indication, type, complications.

Appendix 3 Surgical Wound Classification

The wound classifications listed below are taken from the CDC Guideline for Prevention of Surgical Site Infection.[31]

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 (eg, 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 post-operative infection were present in the operative field before the operation.

Appendix 4 Clinical Laboratory Assessments

Assessments[a]	Pre-operative Screening Visit (Day -30 to -1)	Surgery Day 0	Post-operative Study Visits			
			Day 5 (±2 days) or Day Before Discharge, Whichever Comes First	Day 30 (±3 days)	Study Completion[b] Day 60 (±3 days)	Unscheduled Follow-up (Between Days 5[±2] – 60[±3])
Haematology (blood)						
Haemoglobin	X		X	X		X
Haematocrit	X		X	X		X
Platelet counts	X		X	X		X
Red blood cells	X		X	X		X
White blood cells w. differential[c]	X		X	X	X	X
Clinical chemistry (blood)						
Alanine aminotransferase	X		X	X	X	X
Albumin	X		X	X	X	X
Alkaline phosphatase	X		X	X		X
Aspartate aminotransferase	X		X	X		X
Beta-human chorionic gonadotropin (pregnancy test)[e]	X					
Bicarbonate	X		X	X		X
Bilirubin	X		X	X		X
Blood urea nitrogen	X		X	X		X

Assessments[a]	Pre-operative Screening Visit (Day -30 to -1)	Surgery Day 0	Post-operative Study Visits			
			Day 5 (±2 days) or Day Before Discharge, Whichever Comes First	Day 30 (±3 days)	Study Completion[b] Day 60 (±3 days)	Unscheduled Follow-up (Between Days 5[±2] – 60[±3])
Calcium	X		X	X		X
Chloride	X		X	X		X
Creatinine	X		X	X		X
Glucose	X		X	X		
Potassium	X		X	X		X
Sodium	X		X	X		X
Total protein	X		X	X		X
Other laboratory tests (blood)						
Activated partial thromboplastin time	X		X	X		X
β2-transferrin (CSF)/ β trace protein[d]			X	X	X	X
C-reactive protein	X		X	X	X	X
HbA1c	X					
HIV, HAV, HBV, HCV, HEV, B19V	X				X	
International normalised ratio	X		X	X		X
Other laboratory tests (urine)						

Assessments[a]	Pre-operative Screening Visit (Day -30 to -1)	Surgery Day 0	Post-operative Study Visits			
			Day 5 (±2 days) or Day Before Discharge, Whichever Comes First	Day 30 (±3 days)	Study Completion[b] Day 60 (±3 days)	Unscheduled Follow-up (Between Days 5[±2] – 60[±3])
Beta-human chorionic gonadotropin (pregnancy test)[e]	X	X				

B19V=parvovirus B19; CSF=cerebrospinal fluid; HAV=hepatitis A virus; HbA1c=glycosylated haemoglobin; HBV=hepatitis B virus; HCV=hepatitis C virus; HEV=hepatitis E virus; HIV=human immunodeficiency virus.

[a] Laboratory assessments not covered by the Common Terminology Criteria for AEs (CTCAE) toxicity scale will be evaluated according to normal values assigned by the local laboratory.

[b] Includes for cases of withdraw or discontinuation.

[c] Differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils).

[d] Only in case of CSF leak where CSF is available for testing.

[e] Women of childbearing potential will be required to take a blood beta-human chorionic gonadotropin (β-hCG) test at pre-operative screening and a urine β-hCG test on Day 0. If screening occurred more than 48 hours prior to performing the operation, baseline clinical laboratory values will be measured.

Appendix 5 Toxicity Grading Scale for Laboratory Values

Toxicity Grading Scale[a] for Laboratory Values					
Parameter		Grade[b]			
		1	2	3	4
Haematology					
HgB	Decrease	<LLN – 10 g/dL	<10 – 8 g/dL	<8.0 g/dL	
	Increase	>0 – 2 g/dL above ULN	>2 – 4 g/dL above ULN	>4 g/dL above ULN	
WBC	Decrease	<LLN – 3000/mm^3	<3000 – 2000/mm^3	<2000 – 1000/mm^3	<1000/mm^3
	Increase			>100000/mm^3	
Platelets (decreased)		<LLN – 75000/mm^3	<75000 – 50000/mm^3	<50000 – 25000/mm^3	<25000/mm^3
Clinical chemistry					
Calcium (high)		>ULN – 2.9 mmol/L	>2.9 – 3.1 mmol/L	>3.1 – 3.4 mmol/L	>3.4 mmol/L
Calcium (low)		<LLN – 2.0 mmol/L	<2.0 – 1.75 mmol/L	<1.75 – 1.5 mmol/L	<1.5 mmol/L
Sodium (high)		>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	> 160 mmol/L
Sodium (low)		<LLN – 130 mmol/L		<130 – 120 mmol/L	<130 – 120 mmol/L
Potassium (high)		>ULN – 5.5 mmol/L	>5.5– 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L
Potassium (low)		<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L	<3.0 – 2.5 mmol/L	<2.5 mmol/L
Albumin		<LLN – < 3 g/dL	<3 – 2 g/dL	<2 g/dL	
ALT		>ULN – 3.0 × ULN	>3.0 – 5.0 × ULN	>5.0 – 20.0 × ULN	>20.0 × ULN
Aspartate aminotransferase		>ULN – 3.0 × ULN	>3.0 – 5.0 × ULN	>5.0 – 20.0 × ULN	>20.0 × ULN
Total bilirubin		>ULN – 1.5 × ULN	>1.5 – 3.0 × ULN	>3.0 – 10.0 × ULN	>10.0 × ULN
ALP		>ULN – 2.5 × ULN	>2.5 – 5.0 × ULN	>5.0 – 20.0 × ULN	>20.0 × ULN

Toxicity Grading Scale[a] for Laboratory Values				
Parameter	Grade[b]			
	1	2	3	4
Creatinine	>ULN – 1.5 × ULN	>1.5 – 3.0 × ULN	>3.0 – 6.0 × ULN	>6.0 × ULN
INR	>1 – 1.5 × ULN	>1.5 – 2.5 × ULN	>2.5 × ULN	
aPTT	>ULN – 1.5 × ULN	>1.5 - 2.5 × ULN	>2.5 × ULN	

ALT=alanine aminotransferase; ALP=alkaline phosphatase; aPTT=activated partial thromboplastin time; CTCAE=Common Terminology Criteria for Adverse Events; HgB=haemoglobin; INR=international normalised ratio; LLN=lower limit of normal; ULN=upper limit of normal; WBC=white blood cell.

[a] The National Cancer Institute CTCAE v4.03.

[b] Grade refers to severity: 1=mild, 2=moderate, 3=severe, 4=life-threatening or disabling, 5 (not shown in the table)=death.

Appendix 6 Instructions for Preparation of FS VH S/D 500 s-apr

The shelf life of FS VH S/D 500 s-apr (frozen) in AST is 24 months, provided that the product is shipped and stored at ≤-4°F (-20°C). Thawed, unopened pouches may be stored for up to 4 hours in an incubator at 98.6°F (37°C) until use. If the solution is not used within 4 hours after thawing, FS VH S/D 500 s-apr must be discarded.

Pre-filled syringes are for single use only. Discard any unused product.

The product must not be used after the expiration date indicated on the label.

Procedure for thawing FS VH S/D s-apr (frozen) using incubator (98.6°F [37°C]):
On Day 0 (surgery day), keep the pre-filled syringes in their pouches and place them in an incubator. Remove the pouches from the incubator after thawing and warming. Transfer the inner pouch with the pre-filled syringe onto the sterile field. Maintain the product at 98.6°F (37°C) until use. The product must be used within 4 hours. *(The protective syringe cap should not be removed until thawing is complete and the application tip is ready to be attached).*

Approximate Incubator Thawing and Warming Times	
Incubator (in pouches) at 98.6°F (37°C)	
Pack Size	**Advanced Syringe Technology (AST)**
4 mL	85 minutes

The sealer protein and the thrombin solutions should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Before use, check the thawed product visually for particles, discoloration, or other changes in its appearance. If one of the above occurs, dispose of the solutions.

The thawed sealer protein solution should be liquid but slightly viscous. If the solution has the consistency of a solidified gel, it must be assumed to have become denatured (possibly due to an interruption of the cold storage chain or by overheating during warming). In this case, do not use FS VH S/D 500 s-apr on any account!

Remove the syringe from the bags only shortly before use. Remove the protective caps from the syringes only immediately before application. Use FS VH S/D 500 s-apr only when it is thawed and warmed completely (liquid consistency).

Important Notes:

- Do not use FS VH S/D 500 s-apr (frozen) unless it is completely thawed and warmed (liquid consistency) to 98.6°F (37°C).
- Do not thaw the product by holding it in your hands![25]
- Do not expose to temperatures above 98.6°F (37°C).
- Do not microwave.
- Once thawed, do not refrigerate or re-freeze.

Application:

For application, connect the double chamber ready-to-use syringe with the sealer protein solution and the thrombin solution to a joining piece and an application canula – both are provided in the set with the application devices. The common plunger of the double chamber ready-to-use syringe ensures that equal volumes of the two sealant components are fed through the joining piece into the application canula where they are blended and then applied.

FS VH S/D 500 s-apr is to be applied by dripping in a thin and continuous layer with a 5 mm overlap on each side of the sutured line. Approximately 2 mL of FS VH S/D 500 s-apr will be needed to cover a suture line 10 cm long and a 1 cm wide (10 cm^2) as per the package insert. Keep the dura surface that is adjacent to the suture as dry as possible immediately before and during the application of the IP. In order to ensure adequate mixing, immediately before application, expel the first 5 drops from the syringe, then apply product along the dura suture line. Keep the application speed as constant as possible (ie, 0.5 mL/second). In case the second application is needed, all polymerized product from the first application must be removed before the second application is done.

Appendix 7 Instructions for Preparation of DuraSeal Dural Sealant

The shelf life of DuraSeal Dural Sealant is 12 months, provided that the product is shipped and stored at 77°F (25°C).[27] Application of DuraSeal hydrogel must be completed within 1 hour after preparation. The DuraSeal Dural Sealant System is for single use only. Discard any unused product.

How Supplied

The components of the DuraSeal System are:

- Diluent Syringe (blue label) with white cap (1)
- Powder Vial (1)
- Clear Precursor Syringe with white cap (1)
- Applicator (1)
- Spray Tip (3)
- Plunger Cap (1)
- Syringe Holder (1)

Directions for Use:

The application procedure consists of 3 steps:

A) Preparing the Blue Precursor,

B) Assembling the DuraSeal System Applicator; and

C) Hydrogel Application.

Preparing the Blue Precursor:

Note: Inspect the PEG powder vial to ensure the powder is free-flowing, or can be loosened up by shaking. If the powder remains not free-flowing, discard the entire kit.

1. Open the pouch and introduce the polymer kit tray into the sterile field.

2. Once in the sterile field, remove the lid from the polymer kit tray.

3. Remove and discard syringe cap from Diluent Syringe (blue label).

4. Attach the Diluent Syringe to the Powder Vial.

5. Without depressing the syringe plunger, pierce the vial seal by pushing the syringe into the vial cap until it is fully depressed (twisting is not required). The entire threaded

portion of the vial cap should be depressed below the level of the surrounding plastic vial rim.

6. Inject syringe contents into the vial.

7. Gently shake the vial/syringe assembly until the powder is completely dissolved. The solution will turn blue.

8. Invert the vial/syringe assembly, and draw the vial contents back into the syringe.

9. Unscrew the syringe from the vial and discard the vial.

Assembling the DuraSeal System Applicator

1. Prior to attaching the syringes to the applicator, ensure syringe fluid levels are equal. If fluid levels are not equal, expel fluids out of syringes until equal.

2. Attach blue and clear precursor syringes to the applicator.

3. Attach the syringe holder which slides over both syringe barrels.

4. Carefully attach the Plunger Cap to the plungers of both syringes without dispensing precursors into the applicator. Hold the syringes by the plungers while performing this operation so as to not deliver any of the precursors into the applicator.

5. Attach a spray tip to the applicator.

Note: Avoid touching the Plunger Cap before application to avoid inadvertent precursor injection and tip plugging.

Hydrogel Application

Note: Achieve hemostasis and minimize CSF outflow. Ensure that there are 2 - 3 mm margins around the durotomy edge and that the margins are clear of clots and fluids, hemostatic agents and loose connective tissue.

1. Position the applicator 2 - 4 cm from the target site. Apply firm even pressure to the center of the Plunger Cap to dispense the precursors. Rapid initial spraying, followed by a slower controlled rate is recommended.

2. Continue applying the hydrogel until a thin (1 – 2 mm) coating is formed.

Note: If delivery is interrupted and the spray tip is plugged, remove the spray tip, wipe the applicator tip, attach a new spray tip, and continue delivery.

Note: The blue colour of the hydrogel aids in gauging thickness. As the thickness of the DuraSeal hydrogel increases to 2 mm, the fine epidural vasculature becomes less visible.

Note: Hydrogel application beyond the edges of the dural margin may be removed with scissors or mechanical disruption. Irrigation immediately after the sealant has solidified is permitted.

Storage

The DuraSeal Dural Sealant System should be stored at or below 77°F (25°C).

Appendix 8 Surgical Site Infections (SSIs) – CDC/NHSN Definitions

In this protocol, SSIs will be defined according to the criteria outlined by the CDC and the NHSN (in table below) modified to fit this protocol from www.cdc.gov/nhsn/PDFs/pscManual/9pscSSIcurrent.pdf:[32]

Surgical site infections are divided into 1 of the following types:

1. Superficial incisional SSIs
2. Deep incisional SSIs
3. Organ/space SSIs

Surgical Site Infections – CDC/NHSN Definitions	
Superficial incisional SSI	Superficial incisional SSIs must meet the following criteria: Infection occurs within 30 days after the operative procedure (where Day 1 = the procedure date) **And** Involves only skin and subcutaneous tissue of the incision **And** Patient has at least 1 of the following: 1. Purulent drainage from the superficial incision. 2. Organisms isolated from an aseptically-obtained culture of fluid or tissue from the superficial incision. 3. Superficial incision that is deliberately opened by a surgeon, attending physician or other designee and is culture-positive or not cultured **And** Patient has at least 1 of the following signs or symptoms: pain or tenderness; localised swelling; redness; or heat. A negative culture finding does not meet this criterion. 4. Diagnosis of a superficial incisional SSI by the surgeon or attending physician or other designee.
Comment	There are 2 specific types of superficial incisional SSIs: a. Superficial Incisional Primary – a superficial incisional SSI that is identified in the primary incision in a patient that has had an operation with 1 or more incisions (eg, C-section incision or chest incision for coronary artery bypass grafting surgery [CBGB]). b. Superficial Incisional Secondary – a superficial incisional SSI that is identified in the secondary incision in a patient that has had an operation with more than 1 incision (eg, donor site incision for CBGB).
Exceptions	**The following do NOT qualify as criteria for meeting the NHSN definition of superficial SSIs:** • A stitch abscess alone (minimal inflammation and discharge confined to the points of suture penetration) • A localised stab wound or pin site infection

	• Diagnosis of "cellulitis", by itself, does not meet criterion d for superficial incisional SSIs An infected burn wound is classified as a BURN and is not reportable under this module.
Deep incisional SSI	Deep incisional SSIs must meet the following criteria: Infection occurs within 30 after the operative procedure (where Day 1 = the procedure date) **And** Involves deep soft tissues of the incision (eg, fascial and muscle layers) **And** Patient has at least 1 of the following: • purulent drainage from the deep incision. • a deep incision that spontaneously dehisces or is deliberately opened by a surgeon, attending physician or other designee and is culture-positive or not cultured. **And** • patient has at least 1 of the following signs or symptoms: fever (>38°C); localised pain or tenderness. A culture-negative finding does not meet this criterion. • an abscess or other evidence of infection involving the deep incision that is detected on direct examination, during invasive procedure, or by histopathologic examination or imaging test.
Comments	There are 2 specific types of deep incisional SSIs: 1. Deep Incisional Primary – a deep incisional SSI that is identified in a primary incision in a patient that has had an operation with 1 or more incisions (eg, C- section incision or chest incision for CBGB) 2. Deep Incisional Secondary – a deep incisional SSI that is identified in the secondary incision in a patient that has had an operation with more than 1 incision (eg, donor site incision for CBGB)
Organ/Space SSI	Organ/Space SSIs must meet the following criteria: Infection occurs within 30 days after the operative procedure (where Day 1 = the procedure date) **And** Infection involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure **And** Patient has at least 1 of the following: • purulent drainage from a drain that is placed into the organ/space • organisms isolated from an aseptically-obtained culture of fluid or tissue in the organ/space • an abscess or other evidence of infection involving the organ/space that is detected on direct examination, during invasive procedure, or by histopathologic examination or imaging test.

Comments	Because an organ/space SSI involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure, the criterion for infection at these body sites must be met in addition to the organ/space SSI criteria.

Appendix 9 Sponsor Signatures

Study Title:	A Randomised Controlled Study to Evaluate the Efficacy and Safety of Fibrin Sealant, Vapour Heated, Solvent/Detergent Treated (FS VH S/D 500 s-apr) Compared to DuraSeal Dural Sealant as an Adjunct to Sutured Dural Repair in Cranial Surgery
Study Number:	3599-001
IND Number:	013204
EudraCT Number:	2015-005535-40
Final Date:	Amendment 2, 06 Nov 2017

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: [redacted] Date: [redacted]

[redacted]
Baxter Healthcare Corporation

Signed: _____ Date: _____

[redacted]
Baxter Healthcare Corporation

Signed: _____ Date: _____

[redacted]
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Signed: _____ Date: _____

[redacted]
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[redacted]

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Signed: _____ Date: _____
[redacted]
Baxter Healthcare Corporation

Signed: [redacted] Date [redacted]
[redacted]
Baxter Healthcare Corporation

[redacted]

Appendix 10 Investigator's Signature

Study Title:	A Randomised Controlled Study to Evaluate the Efficacy and Safety of Fibrin Sealant, Vapour Heated, Solvent/Detergent Treated (FS VH S/D 500 s-apr) Compared to DuraSeal Dural Sealant as an Adjunct to Sutured Dural Repair in Cranial Surgery
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EudraCT Number:	2015-005535-40
Final Date:	Amendment 2, 06 Nov 2017

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

<enter name and credentials>
<enter title>
<enter affiliation>
<enter address>
<enter phone number>