Statistical Analysis Plan: 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 ClinicalTrials.gov Identifier: NCT02891070
Study Phase:	Phase 3
Study Design	This study is a phase 3, prospective, controlled, randomized, single-blind (patient) multicenter study to compare effectiveness and safety of FS VH S/D 500 s-apr versus DuraSeal Dural Sealant in a total of 202 evaluable subjects (1:1 randomization) undergoing elective cranial surgery for the treatment of a pathological condition specifically located in the posterior fossa (PF) or supratentorial (ST) regions.
Product Name:	FS VH S/D 500 s-apr
Formulation	Oxidized cellulose
Statistician:	[redacted] Baxter Healthcare One Baxter Parkway Deerfield, IL 60015, USA
Sponsor:	Baxter Healthcare Corporation One Baxter Parkway Deerfield, IL 60015 USA
Responsible Medical Officer:	[redacted]
Final Date:	2017 AUG 10
Version:	2.0

Confidentiality Statement

[redacted]

Table of Contents

List of Appendices

No table of figures entries found.

1. SIGNATURE PAGE

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
Statisticians:	[redacted]

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Prepared by:_____ Date:_____
[redacted]
Baxter Healthcare

Approved by:_____ Date:_____
[redacted]
Baxter Healthcare

Approved by:_____ Date:_____
[redacted]
Baxter Healthcare

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADE	adverse device effect
AE	adverse event
ATC	Anatomical Therapeutic Chemical
CFR	Code of Federal Regulations
CI	confidence interval
CIP	clinical investigation plan
CRO	contract research organization
DSMB	data safety monitoring board
eCRF	electronic case report form
FAS	full analysis set
ICF	informed consent form
IWRS	interactive web-response system
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NMC	non-medical complaint
OC	oxidized cellulose
PPS	per-protocol analysis set
SADE	serious adverse device event
SAE	serious adverse event
SAER	serious adverse event report
SI	serious injury
SD	standard deviation
SE	standard error
TBS	target bleeding site
TTH	time to hemostasis
UADE	unanticipated adverse device effect
WHO	World Health Organization

3. INTRODUCTION

This Statistical Analysis Plan is intended to describe the planned statistical analysis of project 3599-001.

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.

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.

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 fibrin sealant (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.

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.

4. TRIAL 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 tumors, vascular malformations, or Chiari type 1 malformations) specifically in the PF or ST region.

4.1 Primary Objectives

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

4.2 Secondary Objectives

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

4.3 Exploratory Objectives

Not applicable.

5. STUDY DESIGN AND CONDUCT CONSIDERATIONS

5.1 Study Design

This is a phase 3, prospective, randomized, controlled, 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 tumors, 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 randomization 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.

5.2 Baseline definition

Baseline values are not applicable for effectiveness measures. Safety measures of clinical laboratory parameters and vital signs will be evaluated with respect to initial values taken during the screening visit.

5.3 Sample Size

The number of subjects in a clinical trial should always be large enough to provide a reliable answer to the questions addressed. This number is usually determined by the primary objective of the trial. If the sample size is determined on some other basis, then this should be made clear and justified. For example, a trial sized on the basis of safety questions or requirements or important secondary objectives may need larger numbers of subjects than a trial sized on the basis of the primary efficacy question (see ICH E1A).

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 utilizing 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 SAS 9.4 software (SAS Institute; Cary, NC). The primary analysis will be performed on the per protocol analysis set (PPS). Assuming that the PPS is 10% less than the total number of randomized subjects, 112 patients per treatment group should be randomized, and there will be 224 patients in total.

5.3.1 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. Thus, the assumed proportion of [redacted]% for DuraSeal in the current Tisseel study is based on results of this previous study evaluating Adherus and DuraSeal.

5.4 Randomization Procedure

Patients will be randomly assigned to FS VH S/D 500 s-apr or DuraSeal Dural Sealant at a ratio of 1:1. Randomization 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 randomized study population. Randomization will be controlled via an interactive Webresponse 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 maneuver), 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.

5.5 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 H2O 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 H2O

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.

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 will be used to confirm the presence of CSF.

5.6 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]).

Unplanned interventions include meningitis, the management of a deep infection, minimally invasive procedures, and the return to the operating room for neurosurgical complications other than a CSF leak or pseudomeningocele formation, or those related to the subject'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.

5.7 Completion and Discontinuation

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]).

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.

6. STUDY POPULATIONS

6.1 Subject Disposition

The number of subjects who signed informed consent (enrolled), met the pre- and intra-operative inclusion and exclusion criteria (eligible), were randomized, and withdrew early will be displayed for subject disposition. Early withdrawals will be summarized according to reason for withdrawal. Subjects who have been assigned a treatment based on pre-operative criteria, but were found not eligible intraoperatively are not considered to be randomized (for more detail on randomization see section 5.4).

6.2 Analysis Populations

Two types of analyses of effectiveness are planned: analysis of the full analysis set (FAS) and of the per-protocol analysis set (PPS). The primary efficacy analysis will be carried out on the PPS. The analysis using the FAS will be used as a supportive analysis. Assessment of safety will be carried out on all subjects treated (safety analysis set).

- Full analysis set: The FAS will consist of all subjects who were randomized and treated with at least 1 dose of IP/control. Subjects will be analyzed as randomized.

- Per-protocol analysis set: The PPS is defined as a subset of the FAS. Subjects with any major deviation that may impact the primary efficacy parameter will be excluded from the per-protocol analysis set (see section 6.3 for more detail on protocol deviations leading to exclusion).

Safety analysis set: The safety analysis set will consist of all subjects who are treated with IP/Control. Subjects will be analyzed as treated.

6.3 Protocol Deviations

Protocol deviations will be classified as minor or major deviations and reviewed at a data review meeting. Subjects with any major deviation that may impact the primary efficacy parameter will be excluded from the per-protocol analysis set, including the following:

- Violations inclusion and/or exclusion criteria (pre and/or intra-operative assessment)
- Use of prohibited medication known to influence the primary endpoint
- Randomization or treatment errors
- Improper administration of study product
- Improper assessment of the primary endpoint

7. STATISTICAL ANALYSIS

7.1 General

The analyses described in this SAP refer to Amendment 2 of the Clinical Investigation Plan (dated 2015 Nov 09). Unless otherwise noted, all analyses will be performed using [redacted].

treatment group and overall. Safety data will be summarized by actual treatment and overall. Continuous variables will be summarized by the following sample statistics: number of non-missing observations, mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be presented by their absolute frequency and percentage (based on the number of subjects in the respective group).

7.2 Handling of Missing Data

Only subjects for whom endpoint data are available will be included in the statistical analysis. Missing values will be neither replaced nor estimated in the primary analysis.

7.3 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 subjects.

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 subjects have been completed, and will have the discretion to recommend stopping the trial due to safety, efficacy, or futility concerns. The stopping rules are presented in Section 7.4.

7.4 Interim Analysis

An interim analysis will be conducted after the completion of 50% of patients. A group sequential design utilizing O'Brien-Fleming boundaries will be carried out. Basic demographic tables will be produced during the interim analysis. Predicted values for the primary outcome will be produced from a logistic regression equation containing terms for treatment, site and surgical region (supratentorial or posterior fossa). A one-sided two sample t-test will be performed to compare the lower bound of the difference (active – control) between treatments in the mean predicated proportions against the null value of -0.1, to test whether the mean predicted value for Tisseel is less than -0.1 less than the mean predicted value for Duraseal. 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.

7.5 Pooling Strategy for Study Sites

Generally, the data of all study sites will be analyzed together. The logistic regression model for the efficacy analysis will use study site as a factor. In the case of study sites

with fewer than 5 subjects, those study sites may be combined into entities of similar size for the purpose of including in the logistic regression model as a factor.

7.6 Visit Windows/Unscheduled Visits

For tabulation, values will be summarized according to the planned time point as recorded in the eCRF. Data recorded at unscheduled visits will only be listed.

7.7 Other Issues

Not applicable.

7.8 Changes to Planned Analyses Described in the Clinical Investigation Plan

Not applicable.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and baseline variables as collected in the eCRF will be summarized according to the general principles as detailed above. Demographics will include sex, race, ethnicity, age (years), height (cm), weight (kg) and BMI (kg/m^2). Medical history will be coded using MedDRA and incidences will be tabulated by System Organ Class and Preferred Term. Previous medication (stopped before the surgery) and concomitant medication and non-drug therapies (ongoing at the time of surgery or started between surgery and end of study participation) will be coded using WHO Drug Dictionary (medications) and MedDRA (non-drug therapies) and tabulated by ATC Term and Preferred Term.

9. SURGERY DETAILS AND EXPOSURE

The following information on the surgery will be tabulated and/or provided in a listing.

9.1 Planned Surgery Details

- Hospitalization for planned study surgery admission/discharge dates (listing only)
- Duration of hospital stay for planned study surgery (days, to nearest half day)
- Indication for surgery (categories TBD)
- Surgery type [craniotomy with planned durotomy, craniectomy with planned durotomy]
- Surgery region [posterior fossa, supratentorial]

9.2 Intraoperative Details

- Length of sutured durotomy (cm)
- Needle type used for closure (listing only)

  - Atraumatic needle
  - Ethicon (atraumatic needle 12 or 17, fibre 5/0, 70 cm)
  - Type E6 / 0.6x16 (surgical needles)
  - TF taper needle
  - RB-1 needle
  - Cylindric
  - Cylindric taper 17mm (HR17)
  - Round bodied
  - CV-23 Taper ½ 17mm; RB-1 plus 17 mm ½
  - Other (specified)
- Suture material (listing only)
  - Neuolon 4-0 suture
  - Vicril
  - Absorbable (polyglactin)
  - Silk, braided, coated, non-absorbable (polyester)
  - SurgiPro II (Monofilament PP)
  - Ethicon-Ethiban Excel 4.0 PE non-resorbable
  - Other (specified)
- Suture technique (listing only)
  - Continuous simple
  - Continuous locked
  - Interrupted
  - Other (specified)
- Tenting sutures used [yes/no] (listing only)
- Dural material used [yes/no] (listing only)
- Dural closure method
  - Suture + autologous material
  - Suture + non-autologous material
  - Suture + other material
  - Suture only
- Type of material used [autologous, non-autologous, other (specified)] (listing only)
  - If type of material used is autologous, specify [fascia, muscle, pericranium]
  - If type of material used is non-autologous, specify [dura patch, hemostasis matrix, other (specified)]
- Surgery start date/time (first skin cut) (listing only)

- Primary dura closure date/time (listing only)
- Surgery end date/time (last skin suture) (listing only)
- Duration of surgery (min) (date/time of last skin suture – date/time of first skin cut)
- Duration from dural closure to end of surgery (min) (date/time of last skin suture – primary dura closure date/time)
- Drainage left after surgery
- Any surgical complications
- Actual treatment applied
- Number of study product applications
- Start/stop times of study product application(listing only)
- Volume of treatment applied (mL) (listing only)
- Type of CSF leak [spontaneous, following Valsalva] (listing only)
- If applicable, time of Valsalva maneuver (listing only)
- If applicable, time of watertight closure (listing only)
- If applicable, type of leak [overflow, seepage, weeping, sweating] (listing only)
- Rescue therapy needed

9.3 Rescue Therapy Details (listing only)

- Reason for rescue therapy
- Time of rescue therapy
- Time watertight dura closure achieved
- Actions performed to achieve watertight dura closure
- Brand name of material used to achieve water tight dura closure
- Material type
- Suture technique

9.4 Post-operative Clinical Assessment of CSF Leak

The following information will be tabulated and/or provided in a listing, by date/visit of assessment (Visit 3, 4, 5 or Unscheduled).

- CSF Leak observed
- Type of CSF leak, if applicable (listing only)Drain duration (days)
- Output volume (mL)
- Beta2-transferrin result
- MRI/CT Done

- MRI/CT findings, if applicable (listing only)
- Surgical revision required

9.5 Surgical Revision

- Indication for surgical revision (listing only)
- Procedure description (listing only)
- Start date/time:End date/time (listing only)
- Complications associated with surgical revision

9.6 Surgical Site Infection

The following information will be tabulated and/or provided in a listing, by date/visit of assessment (Visit 3, 4, 5 or Unscheduled).

- Signs of surgical site infection observed
- Type of surgical site infection, if applicable

10. EFFICACY

10.1 Primary Efficacy Assessment

The primary efficacy analysis will be carried out on the PPS. The analysis using the FAS will be supportive. 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 H2O 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: $P_{FS} - P_{DS} > -0.10$

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. The null hypothesis will be tested against the alternative using logistic regression, taking into account the following covariates: study center and surgery region (supratentorial or posterior fossa). The method described in reference 1 will be used: The parameters of the fitted logistic regression model will be used to predict the success rate of all subjects for both Tisseel and Duraseal treatment. The average response rate per group will be calculated as well as the difference between the two rates. The standard error of the difference will be derived using the delta method in order to construct a 95% confidence interval. A non-inferiority margin of 10% (the largest clinically acceptable difference) will be used; thus, if the lower bound of the 2 sided 95% CI (based on normal approximation) around the difference in proportions (Tisseel group – Duraseal group) is greater than -10% in the final analysis, Tisseel will be declared non-inferior to Duraseal.

10.2 Secondary Efficacy Assessment

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.

11. SAFETY

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 postoperatively. 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.

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. Clinical laboratory parameters and vital signs will be summarized by visit and treatment group. Absolute values and changes from baseline will be presented. Shift tables for baseline vs. worst post baseline assessment (normal, abnormal/not clinically significant, abnormal/clinically significant) will be generated for laboratory parameters.

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

summarized by SOC, preferred term, severity grade (mild, moderate, and severe) and relatedness to treatment ("possibly related" or "probably related" AEs, and AEs with missing information on relatedness will be considered "related"; "unlikely related" or "not related" AEs will be considered "not related"). 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

12. REFERENCES

1. Covariate-Adjusted Difference in Proportions from Clinical Trials Using Logistic Regression and Weighted Risk Differences, Miaomiao Ge, L. Kathryn Durham, R. Daniel Meyer, Wangang Xie, Neal Thomas, Drug Information Journal vol. 45, no. 4, pp. 481-493, 2011

13. LIST OF TABLES, FIGURES AND LISTINGS

13.1 List of Tables

Applicable Analysis Populations	Table Number	Table Name
NA	14.1.1	Subject Disposition
PPS	14.1.2.1	Demographic and Baseline Characteristics
FAS	14.1.2.2	Demographic and Baseline Characteristics
Safety	14.1.2.3	Demographic and Baseline Characteristics

PPS	14.1.3.1	Vital Signs
FAS	14.1.3.2	Vital Signs
Safety	14.1.3.3	Vital Signs
PPS	14.2.1.1.1	Primary Efficacy Assessment - CSF Leakage, Intra- and Post-Operative
FAS	14.2.1.1.2	Primary Efficacy Assessment - CSF Leakage, Intra- and Post-Operative
PPS	14.2.1.2.1	Primary Efficacy Assessment - CSF Leakage, Intra- and Post-Operative Model Results
FAS	14.2.1.2.2	Primary Efficacy Assessment - CSF Leakage, Intra- and Post-Operative Model Results
PPS	14.2.2.1	Secondary Efficacy Assessments
FAS	14.2.2.2	Secondary Efficacy Assessments
PPS	14.2.3.1	Summary of Planned Surgery Intra-operative Details
FAS	14.2.3.2	Summary of Planned Surgery Intra-operative Details
PPS	14.2.4.1	Summary of Planned Surgery Post-operative Details
FAS	14.2.4.2	Summary of Planned Surgery Post-operative Details
PPS	14.2.5.1	Listing of Observed Post-Operative CSF Leak Details
FAS	14.2.5.2	Listing of Observed Post-Operative CSF Leak Details
Safety	14.3	Secondary Safety Assessments
Safety	14.3.1.1	Summary of Adverse Events
Safety	14.3.1.2	Summary of Adverse Events (Serious and Non-Serious) by System Organ Class and Preferred Term
Safety	14.3.1.3	Summary of Serious Adverse Events by System Organ Class and Preferred Term
Safety	14.3.1.4	Summary of Adverse Events (Serious and Non-Serious) by System Organ Class, Preferred Term and Severity
Safety	14.3.1.5	Summary of Adverse Events (Serious and Non-Serious) by System Organ Class, Preferred Term and Relation to Study Product
Safety	14.3.1.6	Summary of Adverse Events (Serious and Non-Serious) by System Organ Class, Preferred Term and Relation to Study Procedure
Safety	14.3.1.7	Summary of Adverse Events of Special Interest (Serious and Non-Serious) by System Organ Class and Preferred Term
Safety	14.3.1.8	Summary of Adverse Events (Serious and Non-Serious) with Incidence >= 5% by System Organ Class and Preferred Term
Safety	14.3.1.9	Summary of Non-Serious Adverse Events with Incidence >= 5% by System Organ Class and Preferred Term
Safety	14.3.1.10	Summary of Adverse Events Leading to Death by System Organ Class and Preferred Term
Safety	14.3.1.11	Summary of Adverse Events Leading to Withdrawl by System Organ Class and Preferred Term
Safety	14.3.2.1	Listing of Serious Adverse Events
Safety	14.3.2.2	Listing of Adverse Events of Special Interest

Safety	14.3.2.3	Listing of Adverse Events Leading to Discontinuation from the Study
Safety	14.3.4.1.1	Shift Table of Hematology Laboratory Parameters
Safety	14.3.4.1.2	Hematology Laboratory Summary
Safety	14.3.4.1.3	Listing of Abnormal Hematology Laboratory Values
Safety	14.3.4.2.1	Shift Table of Chemistry Laboratory Parameters
Safety	14.3.4.2.2	Chemistry Laboratory Summary
Safety	14.3.4.2.3	Listing of Abnormal Chemistry Laboratory Values
Safety	14.3.4.3.1	Shift Table of Coagulation Parameters
Safety	14.3.4.3.2	Coagulation Laboratory Summary
Safety	14.3.4.3.3	Listing of Abnormal Coagulation Laboratory Values
Safety	14.3.4.4.1	Shift Table of Serology Laboratory Parameters
Safety	14.3.4.4.2	Serology Laboratory Summary

13.2 List of Listings

Listing Number	Listing Name
16.2.1	Subject Disposition
16.2.2	Protocol Deviations
16.2.3	Patients excluded from PP
16.2.4.1	Subject Demographics
16.2.4.2	Subject Vital Signs
16.2.4.3	Subject ECG Results
16.2.4.4	Medical History
16.2.4.5	Concomitant Medications and Non Drug Therapies by Coded Drug Term
16.2.5	Study Treatment Application
16.2.6.2	Planned Surgery Intra-operative Details
16.2.6.3	Rescue Therapy
16.2.6.4	Planned Surgery Post-Operative Details
16.2.6.5	Surgical Revision
16.2.6.6	Surgical Site Infection
16.2.6.7	Other Interventions
16.2.6.8	Hospitalizations
16.2.7	Treatment Emergent Adverse Events
16.2.8.1	Subject Laboratory Hematology Results
16.2.8.2	Subject Laboratory Chemistry Results
16.2.8.3	Subject Laboratory Coagulation Results
16.2.8.4	Subject Laboratory Serology Results