CONFIDENTIAL STATISTICAL ANALYSIS PLAN

A Single-Blinded, Randomized, Controlled Study to Evaluate the Safety and Effectiveness of EVICEL® Fibrin Sealant (Human) Compared to a Hydrogel Sealant as an Adjunct to Sutured Dural Repair

Version: AMENDMENT 1   Date: March 21, 2016

Protocol Number: BIOS-14-002 (Amendment 2, dated Nov 17, 2015)

AUTHENTICATION

The contents of this statistical analysis plan (SAP) adhere to current regulatory guidelines[1,2]. We the undersigned declare that to the best of our knowledge this study will be reported and analysed in accordance with the following SAP.

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CHANGES MADE FROM FINAL VERSION

Due to the fact that the primary endpoint is assessed at the 30-Day post-operative visit, it is anticipated that missing data will occur for this endpoint. Therefore, the statement "It is not anticipated that there will be any data missing for the primary endpoint, but if there is, the analysis for the ITT set will be performed considering missing data as failures" was replaced throughout the document by the following statement: "The analysis for the ITT set will be performed considering missing data as failures."

1. STUDY OBJECTIVES

The objective of this study is to evaluate the safety and efficacy of EVICEL Fibrin Sealant (Human) for use as an adjunct to sutured dural repair in cranial surgery. The effectiveness objective of this study is to evaluate whether EVICEL Fibrin Sealant (Human) is non-inferior to DuraSeal Dural Sealant System (Control) for use as an adjunct to sutured dural repair in cranial surgery.

2. STUDY DESIGN

This is a single-blinded randomized, controlled study evaluating EVICEL as an adjunct to sutured dural closure compared to DuraSeal Dural Sealant System.

Approximately 230 subjects undergoing posterior fossa or supratentorial procedures (craniectomy or craniotomy) will be enrolled in the trial with at least 60 subjects undergoing posterior fossa procedures being randomized.

Upon completion of the sutured dural repair, the closure will be evaluated for intraoperative cerebrospinal fluid (CSF) leakage with a baseline Valsalva maneuver performed to an intra-thoracic pressure between 20-25 cm H_2O for 5-10 seconds. If a spontaneous leak is apparent immediately after dural closure, no Valsalva maneuver will be performed.

Subjects who have a CSF leak will be stratified by surgical procedure, posterior fossa or supratentorial approach, and then randomized to either EVICEL Fibrin Sealant or DuraSeal Dural Sealant System in a 1:1 allocation ratio.

Subjects will be followed post-operatively through discharge and again at 30 (-/+7) days and 60 (-/+14) days post-surgery. For the primary endpoint, the incidence of CSF leaks will be assessed up to the 30 day post-operative follow-up period. The incidence of CSF Leak will also be assessed up to the 60 day post-operative follow-up period. A CSF leak or pseudomeningocele will be reported as detected by any of the following: clinical observation, diagnostic testing, imaging or the need for surgical intervention to directly treat a CSF leak.

Randomization will be used to avoid bias in the assignment of treatment to each subject, to increase the likelihood that attributes of the subject are balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

The Sponsor will provide each study site with two sets (Supratentorial or Posterior Fossa Approach) of computer-generated randomization envelopes, each bearing the sequential subject randomization number, and containing the treatment allocation and stratification. In the event that a potential subject fails intra-

operative criteria and is not randomized to the study, the unused randomization envelope should be returned to the series, and used for the next subject.

3. STUDY ENDPOINTS

The primary endpoint is the proportion of subjects that do not have a CSF leak during surgery and up to the 30-day (-/+ 7) post-operative period. A subject is declared as a success when the following conditions are met:

- absence of intra-operative CSF leak following final Valsalva maneuver, and

- absence of CSF leak or pseudomeningocele in the surgical area during the 30-day (-/+ 7) follow-up period.

A confirmed CSF leak or pseudomeningocele is diagnosed by physical examination, diagnostic testing, imaging study or the need for surgical intervention to directly treat a CSF leak during the 30-day (-/+ 7 days) follow-up at the location where randomized treatment was applied.

In addition, the following safety endpoints will be included in this study:

- Incidence of intra-operative CSF leakage following final Valsalva maneuver;

- Incidence of post-operative CSF leakage within 30 days (±7) post-operatively;

- Incidence of post-operative CSF leakage within 60 (±14) days post-operatively;

- Incidence of surgical site infections (SSI) according to NNIS definition and CDC classification within 30 days (±7) post-operatively;

- Incidence of adverse events, collected from time of randomization, throughout the follow-up period until 60 days (±14) after the procedure.

4. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

Not applicable.

5. ANALYSIS SETS

The following three analysis sets defined:

- Intent-to-treat (ITT) set consists of all enrolled and randomized subjects.
- Per-Protocol (PP) set consists of all ITT subjects who have data available for primary effectiveness endpoint and have no major protocol deviations.
- Safety set consists of all enrolled subjects who receive a study treatment.

The primary endpoint will be analyzed using the ITT and the PP set. However, the primary analysis will be based on the PP set. The ITT analysis will be considered confirmatory.

Major protocol deviations are deviations that have an impact on the primary endpoint, or that have an impact on the randomization assignment. These will be determined prior to database lock.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

6.1   Demographic and other baseline characteristics

Demographic and other baseline data will be summarized descriptively for subjects in each treatment group in the ITT set to assess comparability of treatment groups. The categorical data will be summarized descriptively by frequencies along with the associated percentages. The continuous data will be presented using summary statistics such as number of subjects, mean, standard deviation, minimum, median and maximum.

The following demographic variables will be summarized:

- Age;
- Weight;
- Height;
- Body mass index;
- Gender;
- Race/ethnicity;
- History of SVT, DVT/PE;
- Family history of DVT/PE;
- History of alcohol abuse;
- Smoking status.

In addition, the following screening and baseline data will be collected:

- Physical examination, including documentation of relevant medical and surgical history;
- Complete blood count (CBC) with white blood cell differential, liver function tests and electrolytes;
- Type of pregnancy test done prior to procedure (if applicable);
- Documentation of medical history including all concomitant medications during 24 hours prior to surgery;
- Review of inclusion / exclusion criteria to confirm subject eligibility.

7. PROCEDURE DATA

Procedure data will be summarized descriptively for subjects in each treatment group in the ITT set to assess comparability of treatment groups. The categorical data will be summarized descriptively by frequencies along with the associated percentages. The continuous data will be presented using summary statistics such as number of subjects, mean, standard deviation, minimum, median and maximum.

The following procedure variables will be analyzed:

- Operative procedure, including type of approach, indication for surgery and tumor type and location, if applicable;
- Operating room (OR) time;
- Procedure duration (from first incision to closure completion);

- CSF leak determination;
- Specification of treatment to which subject is randomized;
- For patients treated with EVICEL, the following data will be analyzed for first EVICEL application and second treatment of EVICEL (if applicable): method of EVICEL application, number of layers applied, indication of spontaneous leak observation, indication of Valsalva maneuver performed after randomized treatment application (if applicable), indication of CSF leak detection after Valsalva (if applicable) and definition of leak (if applicable);
- For patients treated with Control (DuraSeal), the following data will be analyzed for first DuraSeal application and second treatment of DuraSeal (if applicable): method of DuraSeal application, number of layers applied, indication of spontaneous leak observation, indication of Valsalva maneuver performed after randomized treatment application (if applicable), indication of CSF leak detection after Valsalva (if applicable) and definition of leak (if applicable);
- Total number of kits used, approximate total amount of randomized treatment used, and derived volume per kit;
- Indication of watertight closure after randomized treatment application;
- Indication of additional treatment application;
- Indication of watertight closure at the end of procedure;
- Indication and specification of additional treatments/rescue therapy applied, such as glues/sealants, sutures, hemostasis matrices, antologous and biologic/non-autologous dural patches.

In addition, the following post-procedure to hospital discharge data will be summarized:

- CSF leak and/or pseudomeningocele determination, along with the identification of the test used for diagnosis;
- Surgical site assessment, including presence of infection (brain abscess, meningitis, and/or surgical site infection), hematoma (intradural, extradural, and/or subcutaneous), and other surgical site experience;
- Wound healing assessment;
- Indication of subject presence and duration in ICU;
- Length of subject hospital stay;
- Laboratory data (complete blood count with differential, liver function tests and electrolytes).

8. EFFECTIVENESS

8.1 General methods of analysis

The Clinical Data Management and Biostatistics groups within Clinical Development at ETHICON will be responsible for the overall analysis of data from this protocol. All analyses/summaries will be produced using SAS® (Version 9.1 (EG) or later).

Effectiveness data will be summarized descriptively for subjects in each treatment group in the ITT set to assess comparability of treatment groups. The categorical data will be summarized descriptively by frequencies along with the associated percentages. The continuous data will be presented using summary statistics such as number of subjects, mean, standard deviation, minimum, median and maximum.

8.2   Primary effectiveness analysis

The primary endpoint is the proportion of subjects that do not have CSF leak during surgery and up to the 30-day ($\pm$7) post-operative period. A subject is declared success when the following conditions are met:

- Absence of intra-operative CSF leak following Valsalva maneuver, and
- Absence of CSF leak or pseudomeningocele in surgical area during the 30-day follow-up period.

The primary effectiveness parameter will be analyzed using the ITT and Per-Protocol analysis sets. The Per-Protocol analysis will be the primary effectiveness analysis.

The analysis for the ITT set will be performed considering missing data as failures; in addition, sensitivity analyses for the ITT set will be performed considering missing data as successes, and, as worst-case, with missing data for the EVICEL® group considered as failures and missing data for the DuraSeal™ group considered as successes.

The statistical hypothesis for testing the treatment difference is presented as follows:

- H_0: $\Delta \leq$ -0.10 tested against the alternative hypothesis

- H_a: $\Delta >$ -0.10.

where:

- Δ is the difference between the success rates of Experimental and Control (Experimental minus Control)

- -0.10 is the non-inferiority difference

- The assumed proportion of successes for Control is 0.95.

P_C is the proportion of success in DuraSeal™ Control subjects and P_E is the proportion of success in EVICEL® subjects.

Two hundred and two (202) evaluable subjects (101 per arm) will achieve 90% power to detect a non-inferiority margin difference in group proportions of -0.10. The proportion of successes in the Control group is 0.95. The proportion of successes in EVICEL® group is assumed to be 0.85 under the null hypothesis of inferiority. The power was computed for the case when the actual proportion of successes in the EVICEL® group is 0.95. The one-sided significance level of the test is 0.025.

If the lower limit of the one-sided 97.5% confidence interval for Δ is greater than -0.10, then it will be concluded that EVICEL® is considered to be non-inferior to DuraSeal™.

For the primary endpoint, the comparability between the surgical procedure (posterior fossa or supratentorial approach) subgroups will be evaluated using a logistic regression analysis, with success/failure for primary endpoint as dependent variable and with surgical procedure, treatment group, and interaction between surgical procedure and treatment group as independent variables included in the model. The interaction terms will be considered significant at 0.15 significance level in the logistic regression model. The effect of select demographics and baseline characteristics on the primary endpoint may also be evaluated. In addition, the primary endpoint will be compared between treatment groups using a Cochran-Mantel-Haenszel (CMH) Chi-square test adjusting for the surgical procedure at 0.05 significance level.

8.3   Secondary effectiveness analysis

No secondary effectiveness data will be collected for this study.

8.4   Analysis of follow-up data

The following follow-up data will be summarized descriptively for 30-day (±7 days) and 60-day (±14 days) visits:

- Re-hospitalizations since previous study visits;
- CSF leak or pseudomeningocele determination data;
- Surgical site assessment data;
- Wound healing assessment data;
- Presence of clinically significant changes to subject since previous study visit (for 30-day only);
- Laboratory data (complete blood count with differential, liver function tests and electrolytes) (for 30-day only).

8.5   Statistical/analytical issues

8.5.1   Handling of dropouts or missing data

The analysis for the ITT set will be performed considering missing data as failures; in addition, sensitivity analyses for the ITT set will be performed considering missing data as successes, and, as worst-case, with missing data for the EVICEL® group considered as failures and missing data for the DuraSeal™ group considered as successes.

If there are incomplete dates and calculations (e.g. time since procedure) are needed, the following rules are used (no rules will be applied for missing years; this data would normally be expected to be queried):

- Missing date which includes the procedure data: the rules below are followed unless the derived date is pre-procedure, when the derived date will be 1 day after the procedure.

- Missing day: 15th used

8.5.2   Interim analyses and data monitoring

No interim analysis will be performed for this study.

8.5.3   Multiple comparison / multiplicity

Not applicable.

9.   SAFETY EVALUATION

9.1   Adverse events

The following will be summarized using the Safety set:

- Adverse events, collected from time of randomization, throughout the follow-up period until 60 days (±14) after the procedure;

- Incidence of intra-operative CSF leakage following final Valsalva maneuver;

- Incidence of post-operative CSF leakage within 30 days (±7) post-operatively;

- Incidence of post-operative CSF leakage within 60 (±14) days post-operatively;

- Incidence of surgical site infections (SSI) according to NNIS definition and CDC classification within 30 days (±7) post-operatively;

- Laboratory data (complete blood count with differential, liver function tests and electrolytes).

9.2   Clinical laboratory evaluation

Blood samples will be taken for Complete Blood Count (CBC) with differential, liver tests and electrolytes.

9.3   Vital signs, physical findings and other observations related to safety

Vital signs will not be collected in this study. A physical exam will be performed and medical/surgical history data will be collected at screening.

9.4   Methods of analysis

All safety variables will be summarized descriptively only, for Safety analysis set. No inferential statistical analysis will be carried out.

Adverse events will be summarized descriptively by the treatment received, using Medical Dictionary for Regulatory Activities (MedDRA) terminology, in SI units.

10. DATA PRESENTATION

The report forms part of an integrated clinical study report. The actual numbering of tables, listings and other outputs may change. Numbering is in accordance with ICH guideline E3[2].

10.1   Procedure or treatment labels

The following labels will be used for all output: **EVICEL** and **DuraSeal**.

10.2   Tables and figures

Data will be tabulated by treatment group and, if appropriate, by visit. Continuous data summaries will present (unless stated otherwise) number of observations, number of missing observations (if there are any), mean, standard deviation, minimum, median and maximum. Categorical data summaries will present the number of observations and the corresponding percentage. The following tables will be produced:

10.2.1 In-text tables and figures

These will be produced for the main report in conjunction with the medical writer. These will include, but will not be limited to:

No	Title of table/figure	Notes
F1	Subject disposition	Based on Table 14.1.1.4
T1	Demographic characteristics – ITT analysis set	Summary of Table 14.1.2.1
T2	Surgical procedure – ITT analysis set	Summary of key items from Tables 14.1.3.1-14.1.3.7
T3	Statistical summary for primary effectiveness endpoint – Per-Protocol and ITT analysis sets (including sensitivity analysis summary)	Summary of Tables 14.2.1.1 and 14.2.1.2
T4	Summary of AEs occurring in >5% of subjects– Safety analysis set	Summary of 14.3.1.3

T=Table   F=Figure

10.2.2 Section 14 tables

Shell tables shown in Appendix 1, according to the code in the 'Shell' column. All table numbers will be prefixed with 14.

No	Title of table/figure	Notes	Shell[1]
1.1	Disposition of subjects, analysis sets and protocol deviations		
1.1.1	Disposition of subjects by centre – ITT set	Includes number withdrawn – by center	DS
1.1.2	Enrollment by center – ITT set	By center	E
1.1.3	Summary of protocol deviations – ITT set	Includes both minor and major protocol deviations	PD
1.1.4	Analysis sets – ITT set		ST
1.2	Baseline data	Excludes baseline data that is also measured post procedure and/or safety data	
1.2.1	Demographics – ITT set	Age, height, weight, BMI – continuous data (c); gender, race, ethnicity, history of SVT, DVT/PE, family history of DVT/PE, history of alcohol abuse, smoking status – all discrete data (d)	DG
1.2.2	Baseline characteristics – ITT set	Presence of relevant history of prior surgery, type of pregnancy test done prior to procedure, indication of any relevant changes in medical history between screening and 24 hours before procedure, and confirmation of subject eligibility (all d)	G1[2]
1.2.3	Physical exam / medical / surgical history – ITT set	Includes frequencies	HX
1.3	Operative data		

[1] Shell: Example table from Appendix 1 (Shell tables). Letters refer to standard output, numbers to project specific output.
[2] For Tables G1, G2, G3 notes will indicate if data is continuous or discrete.

No	Title of table/figure	Notes	Shell[1]
1.3.1	Pre-operative data – ITT Set	Operative procedure, type of approach, indication for surgery, tumor type, if applicable, and tumor location (if applicable) (all d)	G2
1.3.2	Operative data: initial CSF leak determination and randomization data – ITT set	Indication of spontaneous CSF leak observation, indication of Valsalva maneuver performed prior to randomization (if no leak), indication of CSF leak detection after Valsalva (if no leak), specification of treatment to which subject is randomized, and indication of tissue based patch use during primary sutured dural closure – all (d)	G2
1.3.3	Operative data: EVICEL application – ITT set	For patients treated with EVICEL, the following data will be analyzed for first EVICEL application and second treatment of EVICEL (if applicable): method of EVICEL application (standard tip, spray or drip, if applicable, control tip, airless spray tip), number of layers applied, indication of spontaneous leak observation, definition of CSF leak observed (if applicable), indication of Valsalva maneuver performed after randomized treatment application (if applicable), indication of CSF leak detection after Valsalva (if applicable), and definition of leak (if applicable) (all d)	G2
1.3.4	Operative data: DuraSeal application – ITT set	For patients treated with Control (DuraSeal), the following data will be analyzed for first DuraSeal application and second treatment of DuraSeal (if applicable): method of DuraSeal application, number of layers applied, indication of spontaneous leak observation, definition of CSF leak observed (if applicable), indication of Valsalva maneuver performed after randomized treatment application (if applicable), indication of CSF leak detection after Valsalva (if applicable), and definition of leak (if applicable) (all d)	G2
1.3.5	Operative data: watertight closure and other treatment data – ITT set	Total number of kits used, approximate total amount of randomized treatment used, derived volume per kit (all c), indication of watertight closure after randomized treatment application, indication of additional treatment application, and indication of watertight closure at the end of procedure (all d)	G2
1.3.6	Operative data: additional treatments/rescue therapy – ITT set	Indication and specification of additional treatments / rescue therapy applied, such as glues/sealants (EVICEL, DuraSeal, BioGlue, Other), sutures (all d), hemostasis matrices (d) (type (d), width (c), length (c)), antologous (fascia, pericranium, fat, muscle, other), and biologic/non-antologous dural patches (all d)	G2
1.3.7	Operative data timings – ITT set	Time in operating room (c), length of procedure (from first incision to closure completion) (c)	G2
2	Effectiveness data		
2.1	Primary endpoint: success (no CSF leak during surgery and up to 30-day visit)	Includes sensitivity analyses	

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No	Title of table/figure	Notes	Shell[1]
2.1.1	Success (no CSF leak during surgery and up to 30-day visit): primary effectiveness analysis – PP set	Discrete data	G2
2.1.2	Success (no CSF leak during surgery and up to 30-day visit): sensitivity analysis – ITT set	Missing data considered as: -Analysis#1: failures (d) Sensitivity analysis - missing data considered as: -Analysis#2: successes (d); -Analysis#3: failures for EVICEL and successes for DuraSeal (d)	G2
2.2	Follow-up assessments		
2.2.1	Post-surgery to hospital discharge assessment – ITT set	Presence of clinically significant changes to the subject, CSF leak and pseudomeningocele determination, along with the identification of the test used for diagnosis, surgical site assessment, including presence of infection (brain abscess, meningitis, and/or surgical site infection – superficial incisional, deep incisional and/or organ-space), hematoma (intradural, extradural, and/or subcutaneous), and other surgical site experience, wound healing assessment, indication of subject presence (all d) and duration in ICU (c), and length of subject hospital stay (c)	G2
2.2.2	30-day (±7 days) and 60-day (±14 days) follow-up assessments – ITT set	Method of contact with subject, indication of re-hospitalizations since previous study visit, presence of clinically significant changes to subject since previous study visit (for 30-day only), CSF leak and pseudomeningocele determination, along with the identification of the test used for diagnosis, surgical site assessment, including presence of infection (brain abscess, meningitis, and/or surgical site infection – superficial incisional, deep incisional and/or organ-space), hematoma (intradural, extradural, and/or subcutaneous), and other surgical site experience, wound healing assessment (all d)	G2
3	Safety data		
3.1	Adverse Events		
3.1.1	Number of subjects experiencing any during/post treatment AE by category – Safety analysis set		AS
3.1.2	Adverse events (during/post treatment) by subject, MedDRA preferred term and system organ class – Safety analysis set		AM

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No	Title of table/figure	Notes	Shell[1]
3.1.3	Summary of during/post treatment adverse events by subject and coded terms, preferred terms occurring in >=5% of subjects – Safety analysis set		AM
3.1.4	Summary of during/post treatment serious adverse events by subject and coded terms – Safety analysis set	Includes adverse events for which the answer for CRF question "Serious?" in the CRF is "Yes"	AM
3.1.5	Summary of during/post treatment surgical procedure related (possibly, definitely) adverse events by subject and coded terms – Safety analysis set	Includes adverse events for which the answer for CRF item "Relationship to surgical procedure" is "Possibly related" or "Related".	AM
3.1.6	Summary of during/post treatment study treatment related (possibly, definitely) adverse events by patient and coded terms – Safety analysis set	Includes adverse events for which the answer for CRF item "Relationship to study treatment" is "Possibly related" or "Related".	AM
3.2	Laboratory data	Reported in SI units	
3.2.1	Laboratory data: Complete Blood Count - Safety analysis set	At baseline, within 72 hours prior to hospital discharge, and at 30-day follow-up	L
3.2.2	Laboratory data: White Blood Cell Differential - Safety analysis set	At baseline, within 72 hours prior to hospital discharge, and at 30-day follow-up	L
3.2.3	Laboratory data: Liver Function Test and Electrolytes - Safety analysis set	At baseline, within 72 hours prior to hospital discharge, and at 30-day follow-up	L
3.3	Other safety data		
3.3	Other safety data - Safety analysis set	Incidence of intra-operative CSF leakage following final Valsalva maneuver, incidence of post-operative CSF leakage within 30 days (±7) post-operatively, incidence of post-operative CSF leakage within 60 (±14) days post-operatively, incidence of surgical site infections (SSI) according to NNIS definition and CDC classification within 30 days (±7) post-operatively (all d)	G2

Note: '–' indicates a new line in the title.

10.3 Listings

Listings will be presented in centre, subject and visit order. The listings will be produced using the data from all subjects.

The columns indicate the listings that will be included in the report. All data available on the database, with the exception of fields used for administration, e.g. signature fields, will be included in the listing for the report.

Missing data will be shown by a space.

10.3.1 <u>Appendix 16.2 listings:</u>

All listings will be prefixed with 16.2.

No	Title of listing	Notes	CRF Page
1	Disposition of subjects		
1.1	Disposition of subjects	Includes reason for withdrawal and time to withdrawal	46
1.2	Visit dates	Includes informed consent and discharge details Includes derived data: -Nights in hospital -Days from procedure	Various
2	Protocol deviations		
2	Protocol deviations		44 and 45
3	Subjects excluded from the analysis		
3	Definition of analysis sets	As defined in Section 5 of this SAP	
4	Baseline characteristics		
4.1	Demographics, special histories, smoking status, pregnancy test and subject eligibility operative procedure, type of approach, indication for surgery, specification of tumor		3, 4, 5, 10, and 11
4.2	Physical exam / medical / surgical history		6, 7, and 8
4.3	Inclusion and exclusion criteria		2 and 13
4.4	Concomitant medications	Derived data: -Days from procedure to start -Duration of Con Med	39 and 40
5	Surgical details		
5.1	Surgical procedure - re-operative information, timings including operation room and length of procedure, initial CSF leak determination, and randomization data	Includes derived data: -Time in the operating room -Length of procedure	14, 15, and 16
5.2	Surgical procedure – EVICEL application details		17 and 18
5.3	Surgical procedure – DuraSeal application details		17 and 18

No	Title of listing	Notes	CRF Page
5.4	Surgical procedure – watertight closure and amount of treatment used		19
5.5	Surgical procedure – additional treatments / rescue therapy		20 and 21
6	Effectiveness data		
6.1	Effectiveness - primary effectiveness endpoint		
6.1	Primary effectiveness endpoint - Success (no CSF leak during surgery and up to 30-day visit) - PP set and ITT set (sensitivity analysis)	Includes derived data: Missing data considered as: -Analysis#1: failures (d) Sensitivity analysis - missing data considered as: -Analysis#2: successes (d); -Analysis#3: failures for EVICEL and successes for DuraSeal (d)	
6.2	Follow-up assessments		
6.2.1	Post-surgery to hospital discharge assessment		22, 23, 24, 25, 26, and 27
6.2.2	30-day (±7 days) and 60-day (±14 days) follow-up assessments		28, 29, 30, 31, 32, 33, 34, 35, and 36
7	Safety data		
7.1	Adverse event listings (each subject)		
7.1.1	Adverse events	Includes derived data: -Days from procedure to start -Duration of AE	42 and 43
7.1.2	Adverse event comments		43
7.1.3	Adverse events (MedDRA codes)		42 and 43
7.1.4	Serious adverse events		42 and 43
7.2	Laboratory data		
7.2.1	Laboratory data - Complete Blood Count	At baseline, within 72 hours prior to hospital discharge, and at 30-day follow-up	37 and 38
7.2.2	Laboratory data - White Blood Cell Differential	At baseline, within 72 hours prior to hospital discharge, and at 30-day follow-up	37 and 38
7.2.3	Laboratory data – Liver Function Tests and Electrolytes	At baseline, within 72 hours prior to hospital discharge, and at 30-day follow-up	37 and 38
7.3	Other safety data		

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No	Title of listing	Notes	CRF Page
7.3	Other safety data	Includes derived data: -Incidence of intra-operative CSF leakage following final Valsalva maneuver; -Incidence of post-operative CSF leakage within 30 days (±7) post-operatively; -Incidence of post-operative CSF leakage within 60 (±14) days post-operatively; -Incidence of surgical site infections (SSI) according to NNIS definition and CDC classification within 30 days (±7) post-operatively	17, 18, 19, 23, 24, 31, 32, 35, and 36

10.3.2 Data review

Listings will be available for regular listing reviews to be organized by Data Management.

11. REFERENCES

1 ICH harmonised tripartite guideline - Statistical principles for clinical trials (E9) – Step 4, 05 Feb 1998.

2 ICH harmonised tripartite guideline - Structure and contents of clinical study reports (E3) – Step 4, 30 Nov 1995.

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APPENDIX 1: TABLE TEMPLATES (SEE ATTACHED DOCUMENT)

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Superficial Incisional SSI

Infections occur within 30 days after the operation *and* infection involves only skin or subcutaneous tissue of the incision *and* at least *one* of the following:
1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture or fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat *and* superficial incision is deliberately open by surgeon, *unless* incision is culture-negative.
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

Do *not* report the following conditions as SSI:
1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration.
2. Infection of an episiotomy or newborn circumcision site.
3. Infected burn wound.
4. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).

Note: Specific criteria are used for identifying infected episiotomy and circumcision site and burn wounds.

Deep Incisional SSI

Infections occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation *and* infection involves deep soft tissues (e.g., fascial and muscles layers) of the incision *and* at least *one* of the following:
1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative.
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

Notes:
1. Report infection that involves both superficial and deep incisional sites as deep incisional SSI.
2. Report organ/space SSI that drains through the incision as a deep incisional SSI.

Organ/space SSI

Infections occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation *and* infection involves any part of the anatomy (e.g., organs or spaces) other than the incision, which was opened or manipulated during an operation *and* at least *one* of the following:
1. Purulent drainage from a drain that is placed through a stab wound into the organ space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histological or radiologic examination.
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

CLASS I/CLEAN:

An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital and urinary tracts are not entered. Clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow non-penetrating (blunt) trauma should be included in this category if they meet these criteria.

CLASS II/CLEAN-CONTAMINATED:

An operative wound in which the respiratory, alimentary, genital and urinary tract is 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, operations with major breaks in sterile technique or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered.

CLASS IV/DIRTY OR INFECTED:

Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.