Statistical Analysis Plan (SAP)

A Prospective Study Evaluating the Safety and Effectiveness of EVARREST® Fibrin Sealant Patch in Controlling Mild or Moderate Hepatic Parenchyma or Soft Tissue Bleeding During Open Abdominal, Retroperitoneal, Pelvic and Thoracic (Non-Cardiac) Surgery in Pediatric Patients

Protocol Version: BIOS-16-001 Amendment 6 – 2 November 2023

SAP: Original Version (Final) - **SAP Date:** 22OCT2023

SAP Revision: Administrative Change 1 - **SAP Revision Date:** 27FEB2024

The Original Version of this SAP was based on Protocol Amendment 6, dated September 25, 2023. That protocol version was not implemented due to a minor subsequent erorr. It was then signed on Nov 2, 2023 and implemented. This SAP version reflects the implemented protocol date and includes no content changes from the previous SAP version.

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The following individuals have reviewed this version of the Statistical Analysis Plan and are in agreement with the content:

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Revision History

Revision Number	Revision Date (DD/MMM/YYYY)	Reasons for Revision
1.0	22OCT2023	Original Version
2	27FEB2024	Administrative Change 1

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1 Study Design

The objective of this study is to evaluate the safety and hemostatic effectiveness of EVARREST Fibrin Sealant Patch (EVARREST) in controlling mild or moderate soft tissue and parenchymal bleeding during open hepatic, abdominal, pelvic, retroperitoneal, and thoracic (non-cardiac) surgery in pediatric patients.

This is an open-label, multicenter, single-arm study evaluating the safety and effectiveness of EVARREST in controlling mild or moderate bleeding in hepatic parenchyma or soft tissue for which standard methods of achieving hemostasis are ineffective or impractical during surgery in pediatric patients.

For this study, approximately 12 sites in US and UK will be utilized for consecutive screening and enrollment. Subjects will be considered as enrolled when the Informed Consent and Assent Form(s), as appropriate, is signed. Eligible subjects will be treated with EVARREST. Subjects will be followed post-operatively through hospital discharge and at 30 days (±14 days) post-surgery.

At least thirty-five (35) pediatric subjects with an appropriate mild or moderate bleeding TBS will be enrolled in this study. The age of the subjects enrolled in the study will be from 1 month to <18 years. This will include a minimum of 4 subjects aged 1 month (≥ 28 days from birth) to <1 year.

The Target Bleeding Site (TBS) will be the only region evaluated for the primary endpoint and all secondary effectiveness endpoints. The TBS is defined as the first actively bleeding site identified during the soft tissue or hepatic dissection related to the primary operative procedure with challenging mild to moderate bleeding. This site will then be assessed for hemostatic effectiveness after product application as described below.

Once the TBS is identified, the surgeon will immediately apply EVARREST at the actively bleeding TBS. The size of the treatment article applied should be sufficient for coverage of the entire TBS and should overlap the bleeding source with a margin of 0.5-1 inch (1-2 cm).

After placement of EVARREST, the surgeon will apply firm continual manual compression over the entire bleeding area until 4 minutes from TBS identification. The surgeon may use a surgical sponge (laparotomy pad or surgical gauze) to assist in providing adequate pressure over the entire surface area.

Hemostasis is defined as no detectable bleeding at the TBS. Absolute time to hemostasis, defined as the absolute time elapsed from TBS identification to the last moment in time at which detectable bleeding at the TBS is observed, will be recorded.

Hemostasis will be assessed at 4 minutes from TBS identification by carefully releasing manual compression and removing the surgical sponge (if used). Hemostasis will also be assessed at 10 minutes from TBS identification and at initiation of final fascial closure. The absolute time to hemostasis will be recorded. EVARREST should not be removed after bleeding has been stopped.

If bleeding requiring treatment occurs after the 4 minute assessment, the surgeon can retreat the TBS with EVARREST or revert to their standard of care.

Hemostasis will be assessed at 4 minutes and 10 minutes after TBS identification and absolute time to hemostasis is recorded regardless of any additional treatments.

EVARREST can only be used on a single TBS to be evaluated. If additional soft tissue or hepatic parenchymal bleeding sites are identified, the surgeon should treat according to their standard of care.

Primary Endoint:

The primary endpoint in this study will be the absolute time to hemostasis defined as the absolute time elapsed from TBS identification to the last moment in time at which detectable bleeding at the TBS is observed.

Secondary Endoints:

- Proportion of subjects achieving hemostatic success at 4 minutes following TBS identification and no bleeding requiring treatment at the TBS any time prior to final fascial closure
- Proportion of subjects achieving hemostatic success at 10 minutes following TBS identification and no bleeding requiring treatment at the TBS any time prior to final fascial closure
- Proportion of subjects with no re-bleeding at the TBS

Safety Endoints:

- Incidence of adverse events that are potentially related to bleeding at the TBS
- Incidence of adverse events that are potentially related to thrombotic events
- Incidence of re-treatment at the TBS
- Incidence of any adverse events, which will be collected from time of TBS identification, throughout the follow-up period
- Laboratory tests (including hemoglobin, hematocrit, platelets)
- Estimated intra-operative blood loss

- Number and volume of blood products transfused

2 Treatment Assignment

This is a single-arm study in which all subjects will have EVARREST applied at the actively bleeding TBS during the surgical procedure.

3 Randomization and Blinding Procedures

As this is a single-arm study, no randomization will occur, and no blinding procedures are required.

4 Interval Windows

Interval windows for the purpose of analysis in this study will not be defined outside of those for visit scheduling. The final visit occurs approximately 30 days after surgery. There will be a window of 14 days around the scheduling of the 30-day follow-up visit, and any information entered in the eCRFs at this visit will correspond to the associated visit. There will be no assigning of observations to time points outside of the visit to which they are recorded in the eCRFs.

5 Primary and Secondary Endpoints and Associated Hypotheses

Study endpoints are presented under the Study Design section. No hypotheses testing will be performed for this study.

6 Levels of Significance

No formal hypothesis testing will be performed for this study. A two-sided 95% distribution-free confidence interval (CI) for median absolute time to hemostasis will be estimated. In addition, for success/failure secondary endpoints (4 and 10 minutes hemostasis endpoints), two-sided 95% CIs will be estimated for the proportion of successes in EVARREST treated subjects, using the Clopper-Pearson method. All CIs will be estimated for descriptive purposes only.

7 Analysis Sets

The following four analysis sets are defined:

- All Enrolled Set (AES) consists of all subjects who provided informed consent or assent form for this study.

- Full analysis set (FAS or intent-to-treat set) consists of all enrolled and eligible subjects for whom TBS was identified. Subjects who do not complete the procedure after TBS identification will be included in the FAS analysis.

- Evaluable analysis set (or per-protocol [PP] set) consists of all FAS subjects who have no major protocol deviations affecting the primary endpoint and have data available for this endpoint.

- Safety analysis set will consist of all subjects who received treatment.

The primary endpoint analysis will be based on the FAS. An analysis based on the Evaluable set will also be performed for this endpoint, however, it will be considered supportive. Major protocol deviations will be determined prior to database lock.

In addition, for both FAS and Evaluable set, the absolute time to hemostasis will be analyzed descriptively separately for subjects who achieved hemostasis with and without additional treatments being required.

All secondary endpoints will be analyzed using the FAS, while safety endpoints will be analyzed using the Safety analysis set.

8 Sample Size Justification

No formal sample size calculation was performed for this study as no formal statistical hypotheses are being tested. However, a total of 35 subjects with an identified TBS are considered adequate to provide sufficient information to evaluate data descriptively.

9 Analyses to be Conducted

9.1 General Conventions

Categorical variables will be summarized descriptively by frequency counts along with associated percentages. Continuous variables will be summarized descriptively using number of subjects, mean, standard deviation, minimum, median, and maximum. Analyses will be performed using SAS version 9.4 or later. Any final analyses that differ from what has been specified in this document will be identified within the final statistical output and documented within the clinical study report.

9.2 Disposition of Study Subjects

Subject disposition will be summarized using counts and percentages. The number and percentage of subjects completed and discontinued will be tabulated along with the specific reasons for discontinuation.

9.3 Demographic and Baseline Characteristics

Summary statistics of subject demographics (age, gender, race, ethnicity, weight, height, and BMI) will be presented. Similar summaries will also be provided for baseline and surgical characteristics including subject being of child bearing age, surgical procedure, procedure duration, TBS-related data, and other surgical and treatment-related data.

Medical history will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. A listing will be presented for medical history. Surgical history and concomitant medications will be listed only.

9.4 Primary and Secondary Endpoint Analyses

9.4.1 Primary Endpoint Analyses

Descriptive summaries appropriate for continuous data will be provided overall and by pediatric groups (1 month [≥ 28 days from birth] to <1 year, and ≥1 year to ≤18 years) for the primary endpoint, absolute time to hemostasis. Primary endpoint data will also be summarized descriptively for Infants and Toddlers (28 days to 23 months), Children (2 to 11 years) and Adolescents (12 to <18 years).

A two-sided distribution-free 95% CI for median absolute time to hemostasis will be estimated for descriptive purposes only. The following example of SAS code can be used for this purpose:

```
proc univariate data=hemo CIPCTLDF;
var abstime;
run;
```

In addition, absolute time to hemostasis will be analyzed descriptively separately for subjects who achieved hemostasis with and without additional treatments being required.

9.4.2 Secondary Endpoint Analyses

All secondary endpoints, presented in Section 1, will be summarized descriptively using counts and percentages.

In addition, for success/failure secondary endpoints (4 and 10 minutes hemostasis endpoints), two-sided 95% CIs will be estimated for the proportion of success in EVARREST-treated subjects, using the Clopper-Pearson method, for descriptive purposes only.

9.4.3 Safety Analyses

All AEs will be summarized by number of subjects and associated percentage for relationship to the study product and procedure, seriousness, severity, action taken, and outcome. In addition, all AEs reported during the study will be coded to the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. All AEs will be summarized by MedDRA system organ class and preferred term by age group (Infants and Toddlers [28 days to 23 months], Children [2 to 11 years] and Adolescents [12 to <18 years]) and in total, using the number and percentage of subjects. Separate summaries will be provided for product-related and procedure-related AEs. Serious AEs, as well as non-serious AEs, will be summarized in a similar manner. Related events are those where the relationship is indicated as Related or Possibly related.

Laboratory values (including hemoglobin, hematocrit, and platelets) will be listed and summarized descriptively. Changes from baseline will also be summarized. Clinically significant changes will be reported as part of the AE listings.

Estimated intra-operative blood loss will be summarized as a continuous variable. Similarly, the volume of blood product transfused will be summaried as a continuous variable by type of product used.

9.5 Plans for Interim Analysis

No interim analysis will be performed for this study.

9.6 Handling of Missing Data

As the evaluation of the primary endpoint occurs during the study procedure, it is not anticipated that there will be data missing for treated subjects for the this endpoint, but if there is, missing data will not be imputed for the primary analysis. Analyses of secondary endpoints will consider missing data as failures.

9.7 Subgroup Analysis

All subgroup analyses planned for this study are presented in Sections 8.4.1. and 8.4.3.