Statistical Analysis Plan (SAP)

A Prospective, Clinical Study Evaluating the Safety and Haemostatic Effectiveness of SURGICEL®/TABOTAMP® Powder, Absorbable Haemostatic Powder (oxidized regenerated cellulose) in Controlling Mild or Moderate Parenchymal or Soft Tissue Intraoperative Bleeding during General, Gynaecological, Urological, and Cardiothoracic Surgery in Adult Subjects

SURGICEL®/TABOTAMP® Powder in Controlling Mild or Moderate Parenchymal or Soft Tissue Intraoperative Bleeding in Adult Subjects (Europe-PMCF Study)

Protocol Number: BIOS-2017-01

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REVISION HISTORY

Version	[redacted]	List of Changes
1.0		Original Creation of Document

Table of Contents

1 Introduction

This is the Statistical Analysis Plan (SAP) for the final analysis of data collected under Protocol BIOS-2017-01. This SAP describes in detail the statistical methodology and statistical analyses for this protocol.

1.1 **Study Objectives**

The objective of this single-arm, post-market, clinical study is to evaluate the safety and haemostatic effectiveness of SURGICEL Powder in controlling mild or moderate parenchymal or soft tissue bleeding during general, gynaecological, urological, and cardiothoracic surgery in adults.

The primary effectiveness endpoint of this study is:

- The proportion of subjects achieving haemostatic success at **5** minutes following the application of SURGICEL Powder with no re-bleeding requiring additional treatment at the TBS any time prior to initiation of final fascial closure.

The secondary effectiveness endpoints of this study include:

- Proportion of subjects achieving haemostatic success at **3** minutes following the application of SURGICEL Powder with no re-bleeding requiring additional treatment at the TBS any time prior to initiation of final fascial closure;
- Proportion of subjects achieving haemostatic success at **10** minutes following the application of SURGICEL Powder with no re-bleeding requiring additional treatment at the TBS any time prior to initiation of final fascial closure.

The safety endpoints of this study include:

- Incidence of thromboembolic events that were assessed as having either a possible, probable or causal relationship to the study treatment (from time of SURGICEL Powder application at TBS through 30-day follow-up via phone call or office visit);
- Incidence of post-operative re-bleeding that was assessed as having either a possible, probable or causal relationship to the study treatment and requiring medical/surgical intervention (from initiation of final fascial closure through 30-day follow-up via phone call or office visit);
- Incidence of serious adverse events requiring surgical intervention and assessed as having either a possible, probable or causal relationship to the study treatment (from time of SURGICEL Powder application at TBS through 6-month follow-up done via phone call or office visit).

1.2 **Study Design**

This is an open-label, prospective, single-arm, multicentre, multispecialty, post-marketing clinical study evaluating SURGICEL Powder as an adjunct to achieve haemostasis in the control of

capillary, venous, and small arterial haemorrhage when ligation or other conventional methods of control are impractical or ineffective during surgery (open, laparoscopic or thoracoscopic) in adult subjects (18 years or older). Prospective subjects will be informed about the nature of the research, given the informed consent form (ICF) to read, and, if he/she understands the content, he/she will be asked to provide consent by signing the ICF.

Screening will continue until at least 100 evaluable subjects (see definition in section 6) from approximately eight (8) investigational sites (up to 20 subjects for each site) with an appropriate mild or moderate Target Bleeding Site (TBS) are included into the study. The TBS will be defined as the first active bleeding site identified during dissection, related to the primary operative procedure requiring an adjunctive haemostat. The TBS will be the only region evaluated for the primary endpoint and all secondary effectiveness endpoints.

After application of SURGICEL Powder, the TBS will be assessed for haemostasis (no detectable bleeding) at 3, 5, and 10 minutes from application and prior to initiation of final fascial closure in open surgery or port site closure in laparoscopic or thoracoscopic procedures.

All treated subjects will be followed post-operatively through discharge, and via phone call or office visit at 30 days (+14 days) post-surgery. In addition, all treated subjects will receive a 6-month (±30 days) follow-up phone call or office visit to assess the occurrence of any serious adverse event (SAE) requiring surgical intervention and assessed as having either a possible, probable or causal relationship to the study treatment.

2 Treatment Assignment

This is a single-arm study where all enrolled subjects are expected to be treated with SURGICEL Powder to control their mild or moderate parenchymal or soft tissue bleeding during surgery.

3 Randomization and Blinding Procedures

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

4 Interval Windows

Interval windows for the purpose of analysis in this study are not defined outside of those already specified in the protocol for visit scheduling. The protocol Schedule of Activities specifies a window of 14 days after the scheduling of the 30-day follow-up visit (30-day post-surgery +14 days visit) and any information entered in the electronic Case Report Forms (eCRFs) at this visit will correspond to the 30-day visit. Similarly, a window of 30 days is specified around the scheduling of

the 6-month follow-up visit (6-month post-surgery ±30 days) and any information entered in the electronic Case Report Forms (eCRFs) at this visit will correspond to the 6-month visit. There will be no assigning of observations to time points outside of the visit to which they are recorded in the eCRFs.

5 Levels of Significance

No hypotheses are specified for this study and no p-values are being calculated, therefore no level of significance is specified. All estimation of endpoints will be performed using 95% confidence intervals.

6 Analysis Sets

The following three analysis sets are defined:

- Intent-to-Treat (ITT) analysis set consists of all subjects for whom TBS was identified. Subjects who do not complete the procedure with the use of SURGICEL Powder after TBS identification will be included in the ITT.
- Per-Protocol (PP) (Evaluable) analysis set consists of all ITT subjects who have no major protocol deviations affecting the primary effectiveness endpoint and have data available for this endpoint.
- Safety analysis set consists of all subjects who received study product.

The primary effectiveness endpoint will be analysed using the ITT and the PP sets. However, the primary analysis will be based on the ITT set. The PP analysis will be considered supportive.

All secondary effectiveness endpoints will be analysed using the ITT set, while safety endpoints will be analysed using the Safety set.

It is not anticipated that there will be data missing for the primary or secondary effectiveness endpoints, but, if there is, the analyses based on the ITT set will consider missing data as failures for these endpoints. Missing data for safety endpoints will not be imputed.

Major protocol deviations will be determined prior to database lock.

7 Sample Size Justification

No formal sample size determination was performed for this study; however, a sample size of 100 evaluable subjects is considered adequate to provide sufficient information to evaluate the safety and effectiveness outcomes using descriptive summaries. A two-sided Clopper-Pearson

95% confidence interval for the proportion of successes will be reported for the primary effectiveness endpoint. Assuming a success rate of 85%, the estimation precision of the Clopper-Pearson two-sided 95% CI for the success rate (as measured by the half-width of the confidence interval) when the most likely number of successes (85) is observed, is 7.4%.

Additionally, for evaluation of safety and observation of adverse events that occur at a rate as low as 2.5% in the population, a sample size of 100 subjects provides greater than 90% probability for observing at least 1 such adverse event. Thus, a sample size of at least 100 evaluable subjects should give reasonable assurance that the absence of such events in the study is not a result of too few patients being studied, should none be observed.

8 Analyses to be Conducted

8.1 General Conventions

Subject data will be summarized in tables and presented in further detail in listings. All eCRF data will be listed per subject for all subjects. Descriptive statistical analyses will be provided for pre-specified study endpoints. Summaries for continuous variables will include a minimum of number of observations (n), mean, standard deviation, median, minimum, and maximum. Summaries for categorical variables will include number and percentage.

Analyses will be conducted using SAS software. During the course of programming of tables that are mocked up in Appendix I of this SAP, minor modifications may become necessary. Examples of these minor modifications include, but are not limited to, re-wording of a footnote, addition of a footnote, re-labeling of a column, or addition or removal of a column from a listing. In cases where modifications to tables or listings are not related to a change in statistical analysis methodology or conclusions that could be made on the originally proposed methodology, then no amendment of the SAP is necessary. 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.

8.2 Disposition of Study Subjects

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

8.3 Demographic, Baseline, and Surgical Characteristics

Demographic, baseline, and surgical characteristics will be summarized descriptively for all subjects in the ITT set.

Summary statistics of subject demographics (age, gender, childbearing potential, race, and ethnicity) will be presented for the ITT set. Laboratory data (coagulation blood tests - PT, APTT,

and INR), pregnancy test result, physical exam, and background information (type of surgical approach and type of procedure) will be summarized in a similar manner. Medical history will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Surgical characteristics including, at minimum, procedure duration, time in operating room, estimated volume of intra-operative blood loss, blood transfusion data, primary method to obtain hemostasis, TBS dimensions, type of bleeding, TBS tissue type, treatment application details, including additional treatment data, and legth of hospital stay, will be summarized for the ITT set.

8.4 Primary and Secondary Endpoints and Associated Hypotheses

8.4.1 Primary Endpoint and Associated Hypotheses

No formal hypotheses are specified for this study.

The primary performance endpoint is the proportion of subjects achieving haemostatic success at **5** minutes following the application of SURGICEL Powder with no re-bleeding requiring additional treatment at the TBS any time prior to initiation of final fascial closure.

For the primary effectiveness endpoint, the number and percentage of subjects with hemostatic success, as well as the two-sided Clopper-Pearson 95% confidence interval (CI) for the proportion of successes, will be reported for ITT and PP sets. In addition , the primary effectiveness endpoint will be summarized descriptively by bleeding severity (mild and moderate) for the ITT set. Missing outcomes in the ITT set will be treated as effectiveness failures.

8.4.2 Secondary Endpoints and Associated Hypotheses

The following secondary effectiveness endpoints will be analysed descriptively using counts (numbers of subjects with hemostatic success) and percentages, for the ITT set:

- Proportion of subjects achieving haemostatic success at **3** minutes following the application of SURGICEL Powder with no re-bleeding requiring additional treatment at the TBS any time prior to initiation of final fascial closure.
- Proportion of subjects achieving haemostatic success at **10** minutes following the application of SURGICEL Powder with no re-bleeding requiring additional treatment at the TBS any time prior to initiation of final fascial closure.

In addition, a two-sided Clopper-Pearson 95% confidence interval (CI) for the proportion of successes will be reported for secondary effectiveness endpoints. Missing outcomes will be treated as effectiveness failures.

Success/Failure Assessment for the Binary Primary and Secondary Effectiveness Endpoints

- During the 10-minute assessment period and following the initial application of SURGICEL Powder, the surgeon may reapply SURGICEL Powder. The subject will be considered a failure for ***preceding*** binary primary and secondary effectiveness endpoints [e.g. if subjects achieve haemostasis at 3 minutes and re-bleeding occurs at 6 minutes, then the subject will be considered a failure for the ***preceding*** effectiveness endpoints (at 3 and 5 minutes)].
- Reapplication of SURGICEL Powder does not have an impact on the success/failure evaluation of ***subsequent*** binary effectiveness endpoints (e.g. if haemostasis is achieved by reapplication of SURGICEL Powder, the ***subsequent*** binary endpoints will not be impacted. If any additional SURGICEL Powder is applied to the TBS and the TBS is haemostatic at the 10-minute assessment period and maintained up until initiation of final fascial closure, the subject will be considered a success for the effectiveness 10-minute endpoint).
- If during the 10-minute assessment period the TBS requires further haemostatic measures (other than additional application of SURGICEL Powder), the surgeon should perform these measures, and the subject will be considered a failure for all binary primary and secondary effectiveness endpoints (at 3, 5, and 10 minutes).
- Any intra-operative bleeding or any haemostatic measures at the TBS after 10 minutes and prior to initiation of final fascial closure will be considered a failure for all binary primary and secondary effectiveness endpoints.

8.4.3 Additional Endpoints

Counts and percentages will be provided for EUQ (Ease of Use Questionnaire) responses to the questionnaire. All protocol deviations recorded during the study will be classified as minor or major. Counts and percentages will be provided for the type of deviation, the rationale for the deviation, and classification (minor or major).

8.5 Safety Analyses

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

The following specific safety endpoints will be summarized descriptively by presenting the number and percentage of subjects experiencing the occurrence of each event:

- Incidence of thromboembolic events that were assessed as having either a possible, probable or causal relationship to the study treatment (from time of SURGICEL Powder application at TBS through 30-day follow-up via phone call or office visit);
- Incidence of post-operative re-bleeding that was assessed as having either a possible, probable or causal relationship to the study treatment and requiring medical/surgical intervention (from initiation of final fascial closure through 30-day follow-up via phone call or office visit);
- Incidence of serious adverse events requiring surgical intervention and assessed as having either a possible, probable or causal relationship to the study treatment (from time of

SURGICEL Powder application at TBS through 6-month follow-up done via phone call or office visit).

All reported adverse events (AEs) will be summarized by MedDRA system organ class and preferred term. Separate summaries will be provided for device-related and procedure-related AEs. Serious AEs will be summarized in a similar manner. All reported adverse events will be listed.

8.6 Plans for Interim Analysis

No interim analysis for the purpose of altering the study design is planned for this study. Two analyses will be performed. The first analysis will occur after all subjects complete phone call or office visit 1 [30 days (+14 days) post-surgery]. All data collected through 30-day (+14 days) follow-up will be analysed. The second analysis will occur after all subjects complete phone call or office visit 2 [6-month (+/-30 days) post-surgery] and the data collected at this follow-up is available. The second analysis will be performed on the data from the 6-month follow-up assessing any occurrences of SAEs requiring surgical intervention and assessed as having either a possible, probable or causal relationship to the study treatment.

8.7 Handling of Missing Data

It is not anticipated that there will be data missing for the primary or secondary effectiveness endpoints, but, if there is, the analyses based on the ITT set will consider missing data as failures for these endpoints. Missing data for safety endpoints and all other variables will not be imputed and only observed data will be summarized.

8.8 Sensitivity Analyses

No sensitivity analyses are planned for this study.

8.9 Subgroup Analysis

For the primary effectiveness endpoint, the number and percentage of subjects with hemostatic success will be presented separately for subjects with mild bleeding and for subjects with moderate bleeding.

8.10 Assessment of Site Homogeneity

No summaries or adjustments by study site are planned for this study.

8.11 Changes from the Protocol Specified Analysis

-For clarity, “relationship to TBS” was changed to “relationship to study treatment” in the definition of the following safety endpoint: “Incidence of post-operative re-bleeding that was assessed as having either a possible, probable or causal relationship to the study treatment and requiring medical/surgical intervention (from initiation of final fascial closure through 30-day follow-up via phone call or office visit)”.

-For clarity, in the definition of the ITT analysis set, the text “Subjects who do not complete the procedure after TBS identification will be included in the ITT” was changed to to: “Subjects who do not complete the procedure with the use of SURGICEL Powder after TBS identification will be included in the ITT.”

9 Data Monitoring Committee (DMC)

No Data Monitoring Committee was planned or utilized during this study.

Sponsor’s Medical Director (Study Medical Monitor/Safety Lead) will assess all serious adverse events for causality and expectedness and will utilise Ethicon’s Product Safety Committee (PSC) to review and adjudicate the following safety signals:

- Thromboembolic events;
- Postoperative re-bleeding;
- Reoperations for complications assessed as having a possible, probable or causal relationship to the study treatment.

The PSC will also review cumulative safety data from the study. The PSC will advise on the continuing safety of study subjects and those yet to be recruited to the study. Based on cumulative data from the study, the PSC may recommend whether to continue, suspend, modify, or stop the study. At the conclusion of the study, the PSC will give a final assessment of the safety of the product from this study.

Stopping Rules:
The rules outlined below will be used to determine if the clinical trial should be put on hold contingent on PSC recommendations:

- If three confirmed thromboembolic serious adverse events (PE/DVT SAEs) are reported and assessed as being related to the study treatment.
- If one or more subject(s) develops post-operative bleeding and the TBS is confirmed as the cause of the re-bleeding. The relatedness of the SAE to the study treatment is to be determined by the following:
    - Findings at re-operation;
    - Findings of TBS re-bleeding at autopsy (if applicable).

Appendix 1: Table Shells and List of Listings to be Generated

Table shells are provided in Appendix 1 (in a separate document) for all summaries to be generated for this study. These shells are a guide to the general layout of data to be presented. Minor modifications can be made to suit existing programs or macros that are available. Additionally, a list of all listings to be created is provided corresponding to the eCRFs that are used during this study. All fields collected will be listed.

Appendix 1 (in a separate document)

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