STATISTICAL ANALYSIS PLAN

A PROSPECTIVE, RANDOMIZED, CLINICAL STUDY EVALUATING THE SAFETY AND HEMOSTATIC EFFECTIVENESS OF SURGICEL® POWDER ABSORBABLE HEMOSTAT IN CONTROLLING MILD OR MODERATE PARENCHYMAL OR SOFT TISSUE INTRAOPERATIVE BLEEDING DURING GENERAL, GYNECOLOGICAL AND CARDIOTHORACIC SURGERY IN CHINESE ADULT SUBJECTS

BIOS_2017_02

[redacted]

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.1(Dated 07/24/2020) for Protocol BIOS_2017_02

Name	Signature	Date
[redacted]		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

Name	Signature	Date
[redacted]		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.2	07/24/2020	[redacted]	Not Applicable – 1.2 Version

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of data for Protocol BIOS_2017_02. It describes the data to be summarized and analyzed, including specifics of statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 1.1, dated 03/SEP/2019.

2. STUDY OBJECTIVES

The objectives of this 2-arm registration study are to evaluate the safety and to demonstrate non-inferiority of hemostatic effectiveness of SURGICEL Powder compared with SURGICEL Original in controlling mild or moderate parenchymal or soft tissue intraoperative bleeding during general, gynecological, and cardiothoracic surgery in Chinese adult (⩾18 years old) subjects.

2.1. EXPLORATORY OBJECTIVES

Demographic information and data collected in this study may be used in Health Economics and Outcomes Research (HEOR). Examples of exploratory data captured in this study include, but are not limited to, estimated blood loss (EBL), blood transfusion (if applicable), drain usage (if applicable), hemoglobin (Hgb) blood testing, and length of stay (LOS).

In addition, data using the surgeon EUQ (Ease of Use Questionnaire), a tool validated in prior clinical trials, will also be collected and analyzed descriptively.

3. STUDY DESIGN

This is a single blind, prospective, randomized, multicenter, multispecialty, controlled clinical study comparing SURGICEL Powder with SURGICEL Original (control arm) as an adjunct to achieve hemostasis in the control of capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective during surgery (open, laparoscopic, or thoracoscopic) in Chinese adult subjects.

The number of evaluable subjects required for this trial is 210 subjects (105 per treatment arm). In order to account for a potential 10% drop-out rate, at least 234 evaluable subjects (117 per treatment arm) with an appropriate mild or moderate Target Bleeding Site (TBS) will be randomized in a 1:1 allocation ratio to either SURGICEL Powder or SURGICEL Original (control). Randomization will be stratified by investigational site and TBS bleeding severity (mild or moderate bleeding).

Study subjects will be enrolled in approximately 12 study sites. The number of subjects enrolled in any site should not exceed 46 subjects (20% of the total sample size).
After application of either SURGICEL Powder or SURGICEL Original, the TBS will be assessed for hemostasis (no detectable bleeding) at 3, 5, and 10 minutes from application and prior to initiation of final fascial closure on open surgery or port site closure in laparoscopic or thoracoscopic surgical procedures.

All enrolled 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 enrolled subjects will receive a 6-month (+/-30 days) follow-up phone call or office visit to assess the occurrence of any SAE requiring surgical intervention and assessed as possibly related, probably related, or related to the study treatment.

4. PLANNED ANALYSES

4.1. INTERIM ANALYSIS

There are no plans for interim analyses whose intent would be to stop the study early or to adapt the study design or planned number of patients. There will be two planned analysis time points during the study. The first analysis will occur after all subjects complete the phone call or office visit 1 [30 days (+ 14 days) post-surgery]. All data collected through 30-day (+14 days) follow-up will be analyzed.

The second analysis will occur after all subjects complete the 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 possibly related, probably related, or related to the randomized study treatment.

5. ANALYSIS SETS

Agreement and authorization of subjects included/ excluded from each analysis set will be conducted prior to the unblinding of the study.

5.1. ALL SUBJECTS RANDOMIZED SET [RND]

The all subjects randomized (RND) set will contain all subjects who were randomized to study device.

For analyses and displays based on RND, subjects will be classified according to randomized treatment.

5.2. INTENT-TO-TREAT ANALYSIS SET (ITT)

Intent-to-Treat (ITT) analysis set consists of all enrolled subjects for whom TBS was identified. Subjects who do not complete the procedure after TBS identification will be included in the ITT. Subjects were randomized to treatments.

5.3. PER PROTOCOL ANALYSIS SET (PP)

Per-Protocol (PP) analysis set (set of evaluable subjects) consists of all ITT subjects who have no major protocol deviations affecting the primary effectiveness endpoint and have data available for this endpoint.. Subjects will be classified according to randomized treatment.

Major protocol deviations will be determined prior to database lock.

5.4. SAFETY ANALYSIS SET

Safety analysis set consists of all subjects who received study product. Subjects will be classified according to actual treatment received and at least post-baseline follow up.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of

assessments and events.

Reference start date is defined as the surgical procedure day (Day 1 is the day of surgical procedure) and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date, then:

Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date, then:

Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings。

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

6.3. WINDOWING CONVENTIONS

Study procedures and evaluations performed at each visit are included in section 11 of the protocol.

6.4. STATISTICAL TESTS

The default significant level will be 5%; confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

6.5. COMMON CALCULATIONS

The statistical analysis of the data obtained from this study will be performed using SAS® version 9.4 or higher.

Unless otherwise specified, descriptive statistics for continuous variables will be presented using the number of non-missing observations, mean, standard deviation, median, minimum and maximum. In general, the same number of decimal places as in the raw data will be presented when reporting minimum and maximum, one more decimal place than in the raw data will be presented when reporting mean and median, and two more decimal places than in the raw data will be presented when reporting standard deviations. If the raw data have three or more decimals, three decimals will be presented for mean, median, minimum and maximum, and standard deviation.

For categorical endpoints, descriptive statistics will be presented using the frequency counts and percentage of subjects in the various categories of the variable. All percentages will be presented with one decimal, except percentages less than one, which should be presented with 2 decimals or more, as appropriate.

7. STATISTICAL CONSIDERATIONS

For the primary or secondary effectiveness endpoints, the analyses based on the ITT set will consider missing data as failures. Missing data for safety endpoints will not be imputed.

8. OUTPUT PRESENTATIONS

The template provided jointly with SAP describes the output presentation of this study. The format and content of summary tables, graphs and lists are provided by Kuntuo Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

Subject disposition and withdrawals, and protocol deviations , including inclusion and exclusion criteria, will be presented for all subjects.

The assignment of subjects to analysis populations, completion of study/ premature termination of study and protocol deviations/other reasons for exclusion from analysis sets will be summarized in frequency tables. Detailed information will be provided in listings.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized descriptively as described in section 6.5. Demographic characteristics, such as age, gender, and race, will be summarized for the ITT set. In addition, the descriptive statistics for other baseline characteristics will include, but will not limited to medical/surgical history, concomitant medications, and various laboratory data, and will be presented for the Safety analysis set.

Detailed information will be provided in listings.

11. PRIOR MEDICAL /SURGICAL HISTORY

A pre-existing condition is one that is present at the start of the study and is to be reported as part of the subject's medical history. It must be reported as a new Adverse Event if the intensity, frequency, or the character of the condition worsens during the study treatment.

Relevant information in this section will be presented to the Safety set and described separately by treatment group.

12. CONCOMITANT MEDICATIONS

Indication and start-stop dates of concomitant medications administered from 24 hours prior to surgery up to the 30-day follow-up phone call or office visit will be documented on the Concomitant Medication eCRF. This will include medications used chronically (even if temporarily halted for surgery) and those medications administered as a prophylactic before, during and after surgery.

Anesthetics used for study surgery and over the counter (OTC) drugs will not be recorded as concomitant medication. Concomitant medications used to treat Adverse Events (even if the concomitant medication is an OTC drug or nutritional supplement) must also be documented.

Concomitant medications will be presented for the Safety set and will be summarized separately by treatment group.

13. EFFECTIVENESS OUTCOMES

13.1. PRIMARY EFFECTIVENESS ENDPOINT

The primary effectiveness endpoint is defined as the proportion of subjects achieving hemostatic success at 5 minutes following the application of SURGICEL Powder or SURGICEL Original with no

re-bleeding requiring additional treatment at the TBS any time prior to initiation of final fascial closure.

13.1.1. ANALYSIS OF PRIMARY EFFECTIVENESS ENDPOINT

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

The statistical hypothesis for testing the treatment group difference for primary effectiveness endpoint is presented as follows:

H_0: $P_T - P_C \leqslant -0.1$ tested against the alternative hypothesis

H_1: $P_T - P_C > -0.1$.

P_C is the proportion of successes in Control group, and P_T is the proportion of successes in Test group.

Two hundred and ten (210) evaluable subjects (105 per study arm) will achieve 80% power to detect a non-inferiority margin difference in group proportions of 0.1 using a Farrington-Manning score test with a one-sided significance level of 0.025. The proportion of successes in the Control group is assumed to be 0.8. The proportion of successes in Test group is assumed to be 0.7 under the null hypothesis of inferiority. The power was computed for the case when the actual proportion of successes in the Test group is 0.85.

For the primary effectiveness endpoint, a one-sided 97.5% confidence interval for $P_T - P_C$ will be constructed using the Farrington-Manning (FM) score method. If the lower limit of the one-sided 97.5% confidence interval is greater than -0.1, then it will be concluded that the SURGICEL Powder is non-inferior to SURGICEL Original. If the non-inferiority of SURGICEL Powder is established, the superiority of SUGICEL Powder to SURGICEL Original will then be evaluated; if the lower limit of one-sided 97.5% confidence interval is greater than 0, then it will be concluded that the SURGICEL Powder is superior to SURGICEL Original. In addition, two-sided 95% confidence intervals for the proportion of successes in each treatment group separately will be constructed using the Clopper-Pearson method.

Within each TBS bleeding severity level (Mild, Moderate), the primary effectiveness endpoint will be summarized descriptively by treatment group and overall, using frequency counts and associated percentages.

In In addition, a sensitivity (secondary) analysis for the primary effectiveness endpoint will be performed to evaluate the comparability across the 2 strata by using a logistic regression model, with success/failure for primary endpoint as dependent variable and with stratification factor (mild/moderate), treatment group and interaction between stratification factor and treatment group as independent variables included in the model.

An example of SAS code is provided below:

```
proc logistic data=primaryend;

class treatment success;

model success= treatment strata treatment*strata / expb;

run;
```

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

13.2. SECONDARY EFFECTIVENESS ENDPOINT

The following secondary efficacy endpoints are included:

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

13.2.1. ANALYSIS OF SECONDARY EFFICACY VARIABLES

The secondary effectiveness endpoints will be summarized descriptively by treatment group and overall, using frequency counts and associated percentages, for the ITT analysis set.

For the binary (success/failure) secondary effectiveness endpoints (3 and 10 minutes hemostasis endpoints), within-treatment group two-sided 95% confidence intervals will be reported for the proportion of successes using the Clopper-Pearson method. A two-sided 95% confidence interval for the difference in proportion of successes between treatment groups (Test minus Control) will also be calculated for each binary secondary effectiveness endpoint using the FM score method; however, no testing for non-inferiority will be carried out.

In addition, within each TBS bleeding severity level (Mild, Moderate), the binary secondary effectiveness endpoints will be summarized descriptively by treatment group and overall, using frequency counts and associated percentages.TO consult Farrington-Manning（FM）1 method to calculate the percentage difference and the confidence interval through the following procedure:

```
proc freq data=raw1;
tables trt*ae1or0 / riskdiff(cl=FM) nopercent nocol;
run;
```

14. SAFETY OUTCOMES

14.1. . SAFETY ENDPOINTS

The following safety endpoints will be included in this study:

- Incidence of thromboembolic events that were assessed as possibly related, probably related, or related to the study treatment (from enrollment through the 30-day follow-up phone call or office visit);
- Incidence of post-operative re-bleeding that was assessed as possibly related, probably related, or related to the study treatment and requiring medical/surgical intervention (from initiation of final fascial closure through the 30-day follow-up phone call or office visit);
- Incidence of SAEs requiring surgical intervention and assessed as possibly related, probably related, or related to the study treatment (from enrollment through the 6-month follow-up phone call or office visit).

14.1.1. ANALYSIS OF SAFETY ENDPOINTS

All AEs reported during the study will be coded to the Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be summarized descriptively by MedDRA system organ class and preferred

term in each treatment group and in total.

Incidence of AEs will also be summarized descriptively by relationship to study surgical procedure, relationship to the study product, severity, and seriousness.

The specific safety endpoints and other adverse events will be summarized descriptively in each treatment group and overall by presenting the number and percentage of subjects experiencing the occurrence of each event.

In addition, within each TBS bleeding severity level (Mild, Moderate) and overall, the specific safety endpoints listed in section 14.1 will be summarized descriptively by treatment group and overall, using frequency counts and associated percentages.

All outputs for safety outcomes will be based on the Safety analysis set.

14.2. ADVERSE EVENT

For this study, an AE is defined as an untoward medical occurrence (sign, symptom or disease) in a subject or clinical trial subject and which does not necessarily have a causal relationship with the study medical device. An untoward medical occurrence includes any new, undesirable medical experience or worsening of a pre-existing condition.

Enrollment through the 30-Day Follow-Up: All AEs, whether attributable to the device/procedure or not, are to be recorded in the eCRF and reported to the Sponsor.

If a subject reports the same AE more than once within that SOC/PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 as defined in the Data Management Plan.

Incidence for the following adverse events will be summarized by system organ class, preferred term and treatment based on the safety analysis set. Subjects are counted only once within each system organ class and each preferred term.

- All serious adverse events.
- All adverse events.
- All adverse events by maximum severity in the following order: severe, moderate and mild (if severity is missing, the adverse event will be considered as severe for summary tables and will be presented in the data listing with a missing severity)
- All adverse events by strongest relationship to study device in the following order: Related, Probably Related, Possibly Related, Unlikely Related, Not Related (the relationship to study drug will be determined by investigators). If causality is missing, the adverse event will be considered probably related for summary tables, but will be presented in the data listing with a missing relationship.
- All adverse events leading to discontinuation of study treatment.

All adverse events, serious adverse events, deaths, and adverse events leading to discontinuation of study device will be listed in by-subject listings separately.

14.3. DEVICE DEFICIENCY

Detailed information will be provided in listings.

14.4. PHYSICAL EXAMINATION

Actual values and the change from baseline to each scheduled visit in Temperature, BP, HR, RR test results will be summarized for the Safety set by treatment and scheduled visit.

Detailed information will be provided in listings.

14.5. CBC、HGB

Actual values and the change from baseline to each scheduled visit in CBC、HGB test results will be summarized for the Safety set by treatment and scheduled visit.

Detailed information will be provided in listings.

14.6. BLOOD TRANSFUSION

Actual values and the change from baseline to each scheduled visit in BLOOD TRANSFUSION test results will be summarized for the Safety set by treatment and scheduled visit.

Detailed information will be provided in listings.

14.7. 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 possibly related, probably related, or related to the study treatment and requiring medical/surgical intervention (from initiation of final fascial closure through the 30-day follow-up phone call or office visit)”.

-The text defining the PP set and major protocol deviations was changed from:

“Per-Protocol (PP) analysis set (set of evaluable subjects) consists of all ITT subjects who have no major protocol deviations and have data available for primary effectiveness endpoint. Subjects will be classified according to randomized treatment. Major protocol deviations are deviations that have an impact on the primary effectiveness endpoint. These will be determined prior to database lock.”

to:

“Per-Protocol (PP) analysis set (set of evaluable subjects) consists of all ITT subjects who have no major protocol deviations affecting the primary effectiveness endpoint and have data available for this endpoint. Subjects will be classified according to randomized treatment. Major protocol deviations will be determined prior to database lock.”

This change is required to maintain consistency with the manner in which the assessment of the major protocol deviations was performed for this study - major deviations that do not affect the primary effectiveness endpoint did not exclude subjects from the PP set.

The text defining the SS set was changed from:

“Safety analysis set consists of all subjects who received study product. Subjects will be classified according to treatment received.”

to:

“Safety analysis set consists of all subjects who received study product. Subjects will be classified according to actual treatment received and at least post-baseline follow up”