



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

**The SURGICEL® Powder Mild or Moderate Parenchymal or Soft Tissue
Intraoperative Bleeding (China Study)
BIOS_2017_02**

Name of investigational product	SURGICEL® Powder Absorbable Hemostat
Model/Specification	Study group: 3013SP, 3123SPEA Control group: 1953
Management category of product	Class III medical device that needs the approval for clinical trial Y N√ Similar product in same category in China Y√ N
Protocol version number	1.1
Protocol date	03 Sep 2019
Clinical trial leading institution	Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine
Lead Investigator	
Sponsor	ETHICON, LLC.
Agent	Johnson & Johnson Medical (Shanghai) Ltd.

CONFIDENTIALITY STATEMENT

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Revision Record

Revised version	Revised date	Description of changes
1.0 (Original)	03 Jul 2018	Final Protocol
1.1	03 Sep 2019	Amendment

Protocol Approval Form

Protocol Number:	BIOS_2017_02
Protocol Title:	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
Protocol Date:	03 Sep 2019

Author:

	Name	Signature	Date

Approvals:

Title	Name	Signature	Date

COMPLIANCE STATEMENT

This study will be conducted in compliance with the Declaration of Helsinki as well as all applicable local regulations.

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SYNOPSIS

Study Title	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
Short Title	The SURGICEL® Powder Mild or Moderate Parenchymal or Soft Tissue Intraoperative Bleeding (China Study)
Protocol Number:	BIOS_2017_02
Indication	SURGICEL® Powder Absorbable Hemostat (oxidized regenerated cellulose) – [herein – SURGICEL Powder] is used adjunctively in surgical procedures to assist in the control of capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective.
Control:	SURGICEL® Original
Study Objectives	The objectives of this two-arm registration clinical study are to evaluate the safety and to demonstrate non-inferiority of hemostatic effectiveness of SURGICEL Powder compared with SURGICEL® Original (herein – 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.
Location and Number of Study Sites	Approximately 12 sites in China
Number of Subjects	At least 234 randomized subjects (117 per treatment arm)

<p>Study Design</p>	<p>This is a single blind, randomized, prospective 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.</p> <p>After application of either SURGICEL Powder or SURGICEL Original, the target bleeding site (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 procedures.</p> <p>All enrolled subjects will be observed post-operatively through discharge and followed up at 30 days (+14 days) and at 6 months (+/-30 days) post-surgery via phone call or office visit.</p>
<p>TBS Definition</p>	<p>The TBS will be defined as the first accessible bleeding site requiring an adjunctive hemostat to assist in the control of mild or moderate capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective. As a frame of reference, only target bleeding sites with mild or moderate bleeding as defined by the following scale of bleeding intensity will be included:</p> <p>Mild Bleeding: a TBS with a small area of capillary, arteriole, or venule oozing.</p> <p>Moderate Bleeding: a TBS with a larger area of capillary, arteriole, or venule oozing that presents a significant challenge because of the larger area involved, increasing the volume of blood loss,</p> <p><i>or</i></p> <p>A TBS with bleeding that is more pronounced than oozing, which could also come from a small artery or vein, but is not massive, pulsatile, and flowing.</p> <p>Severe Bleeding (excluded from this protocol): (arterial, venous, or mixed) that is rapidly flowing, pulsatile, or spurting, which in the surgeon's judgment, requires rapid control to prevent hemodynamic</p>

	<p>consequences (e.g., hypovolemia, tachycardia, or hypotension) and could involve major volume loss that if not treated rapidly could be life threatening.</p> <p>Note: SURGICEL Powder and SURGICEL Original should NOT be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial or venous bleeding or major defects in arteries and veins.</p>
<p>Procedure Description</p>	<p>The surgeon will use his/her standard surgical techniques for the surgical procedure. The TBS will be defined as the first accessible bleeding site identified during dissection, related to the primary operative procedure requiring an adjunctive hemostat.</p> <p>Once the TBS is identified and conventional techniques were considered impractical or ineffective, the surgeon will define the bleeding severity and immediately randomize the subject. The bleeding severity will describe the intensity of the bleeding that is present at the TBS at the time the surgeon determines that an adjunctive hemostatic product is required. Subjects will be randomly assigned to either SURGICEL Powder or SURGICEL Original (control arm) in a 1:1 allocation ratio. Randomization will be stratified by investigational site and bleeding severity: mild or moderate bleeding.</p> <p>SURGICEL Powder and SURGICEL Original should be applied according to the Instructions for Use (IFU) and/or Investigator Brochure (IB).</p> <p>In the event of continued bleeding or re-bleeding at the TBS at any time prior to closure, the surgeon may add additional SURGICEL Powder or SURGICEL Original (depending on randomization), if clinically appropriate, or revert to their institutional standard of care (SOC).</p> <p>If additional bleeding sites are identified intra-operatively, the surgeon should treat them according to their institution's SOC. However, the TBS will be the only site assessed for hemostatic effectiveness.</p>

<p>Surgical Procedures</p>	<p>Open, laparoscopic, or thoracoscopic surgical procedures with a mild or moderate parenchyma or soft tissue identifiable TBS may be performed.</p> <p>Surgical procedures may include the following:</p> <ul style="list-style-type: none"> • General • Gynecological • Cardiothoracic. <p>Examples of types of surgical procedures considered for this study include, but are not limited to, the following: colectomy, low anterior resections, retroperitoneal tumor resection, liver resection, soft tissue bleeding after adhesiolysis, hernia repair, radical hysterectomy, lymphadenectomy, tumor removal surgery, diffuse bleeding on visceral or parietal pleura, and soft tissue in cardiothoracic procedures.</p>
<p>Study Product Description</p>	<p>SURGICEL Powder is oxidized regenerated cellulose (ORC) prefilled in an applicator to dispense on a TBS or site of bleeding.</p> <p>The SURGICEL Endoscopic Applicator is intended for use in delivering SURGICEL Powder to bleeding surgical sites through a 5mm or larger trocar.</p> <p>SURGICEL Original is a sterile absorbable knitted fabric produced by the controlled oxidation of regenerated cellulose.</p>

<p>Study Endpoints</p>	<p>Primary Effectiveness Endpoint:</p> <ul style="list-style-type: none"> Proportion of subjects achieving hemostatic success at <u>5 minutes</u> 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. <p>Secondary Effectiveness Endpoints:</p> <ul style="list-style-type: none"> Proportion of subjects achieving hemostatic success at <u>3 minutes</u> 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 <u>10 minutes</u> 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. <p>Safety Endpoints:</p> <ul style="list-style-type: none"> Incidence of thromboembolic events that were assessed as possibly 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 or related to the TBS 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 or related to the study treatment (from enrollment through the 6-month follow-up phone call or office visit).
<p>Inclusion Criteria</p>	<p><i>Pre-operative:</i></p> <p>1. Adult subjects aged ≥ 18 years requiring</p>

	<p>elective/non-emergent open or laparoscopic general, gynecological, or cardiothoracic surgical procedures.</p> <ol style="list-style-type: none"> 2. Subject or authorized representative has signed the approved Informed Consent. 3. Subject(s) whose platelet count is $\geq 100,000$ per microliter and International Normalized Ratio (INR) is < 1.5 prior to 24 hours of surgery. <p><i>Intra-operative:</i></p> <ol style="list-style-type: none"> 4. Presence of an appropriate TBS identified intra-operatively by the surgeon. 5. Subject(s) undergoing cardiothoracic surgery with anticoagulation must have anticoagulation reversed prior to TBS identification and treatment.
Exclusion Criteria	<p><i>Pre-operative:</i></p> <ol style="list-style-type: none"> 1. Female subjects who are pregnant or nursing. 2. Subject on heparin within 12 hours prior to surgery, or oral Coumadin (warfarin) and/or Factor Xa inhibitors within 3 days prior to surgery. 3. Subject on antiplatelet/P2Y12 inhibitors medication 5 days prior to surgery; 4. Subject is currently participating or plans to participate in any other investigational product or drug trial without prior approval from the Sponsor. 5. Subjects who are known, current alcohol and/or drug abusers. 6. Subjects with any pre-operative findings identified by the surgeon that may preclude conduct of the study procedure. <p><i>Intra-operative:</i></p> <ol style="list-style-type: none"> 7. Subjects with any intra-operative findings identified by the surgeon that may preclude the use of study product. 8. Subject with TBS in an actively infected field (Class III Contaminated or Class IV Dirty or Infected; see Appendix 1). 9. TBS is on arteries or veins where application of SURGICEL Powder would present a risk of introducing the study product into an open blood vessel.

	<p>10. Major arterial or venous bleeding or major defects in arteries and veins.</p> <p>11. TBS where silver nitrate or any other escharotic chemicals have been applied.</p> <p>12. TBS is in, around, or in proximity to foramina in bone, or areas of bony confine, the spinal cord, or optic nerve and chiasm.</p>
Study Duration	<p>All enrolled subjects will be followed post-operatively through discharge and again at 30 days (+14 days) and 6 months (+/-30 days) post-surgery.</p>
Safety	<p>Sponsor's Medical Director (Study Medical Monitor/Safety Lead) will assess all SAEs for causality and expectedness and will utilize Ethicon's Product Safety Committee (PSC) to review and adjudicate the following safety signals:</p> <ul style="list-style-type: none"> • Thromboembolic events. • Postoperative re-bleeding. • Reoperations for complications assessed as possibly related or related to the study treatment. <p>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 also give a final assessment of the safety of the product from this study. The composition, responsibilities, frequency of PSC meetings, handling of emergency situations, and documentation of PSC meetings will be specified in the Safety Management Plan (SMP).</p> <p>Stopping Rules:</p> <p>The rules outlined below will be used to determine if the clinical trial should be put on hold contingent on PSC recommendations.</p> <ol style="list-style-type: none"> 1. If three confirmed thromboembolic SAEs (pulmonary embolism [PE] / deep vein thrombosis [DVT]) are reported and assessed as being related to SURGICEL Powder.

	<p>2. 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 SURGICEL Powder is to be determined by the following:</p> <ul style="list-style-type: none"> ○ Findings at re-operation. ○ Findings of TBS re-bleeding at autopsy (if applicable).
Exploratory Data	<p>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, length of stay (LOS).</p> <p>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.</p>
Statistical Design	<p>This is a non-inferiority trial with a 10% margin and the statistical analysis comparing treatment groups for primary effectiveness endpoint performed at one-sided significance level of 0.025 and 80% power. The true success rates are assumed to be 85% in the SURGICEL Powder (Test) group and 80% in the SURGICEL Original (Control) group.^{14, 15, 16, 17}</p>
Study Hypothesis	<p>The statistical hypothesis for testing the treatment group difference for primary effectiveness endpoint is presented as follows:</p> <ul style="list-style-type: none"> • $H_0: P_T - P_C \leq -0.1$ tested against the alternative hypothesis • $H_1: P_T - P_C > -0.1$ <p>where:</p> <p>The assumed proportion of successes for Control is 0.8.</p> <p>P_C is the proportion of successes in Control group and</p> <p>P_T is the proportion of successes in Test group.</p>
Sample Size	<p>The number of evaluable subjects required for this trial is 210 subjects (105 per treatment arm). To account for a potential 10% drop-out rate, at least 234 subjects (117 per treatment arm) will</p>

	<p>be randomly assigned in a 1:1 allocation ratio SURGICEL Powder to SURGICEL Original.</p> <p>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.</p>
Statistical Analysis	<p>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 SURGICEL 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.</p> <p>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.</p> <p>In addition, all effectiveness and safety endpoints will be summarized descriptively for subjects in each treatment group. and</p>

	<p>overall. The continuous data will be summarized by number of subjects, mean, standard deviation (SD), median, minimum and maximum. The categorical data will be summarized by frequency counts along with associated percentages.</p>
Interim Analysis	<p>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 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 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 or related to the randomized study treatment.</p> <p>The clinical study report (CSR) will be submitted to investigative sites and CFDA after the first analysis is completed. The CSR will include all primary and secondary endpoints as well as safety endpoints and data through the 30-day follow-up.</p> <p>An addendum to the CSR will be generated and ready for submission after the second analysis is complete, which will include data from the 6-month follow-up assessing any occurrences of SAEs requiring surgical intervention and assessed as possibly related or related to the randomized study treatment.</p>

Table 1: Schedule of Activities

Procedures	Screening within 21 days of procedure ¹	Baseline within 24 hours prior to procedure	Surgical procedure	Post-surgery to hospital discharge	30-Day F/U call or visit (+14 days)	6-Month F/U call or visit (±30 days)
Inclusion/exclusion	X	X	X			
Informed consent	X					
Demographics	X					
Medical/surgical history	X	X ³				
Concomitant medications		X	X	X	X	
Physical exam (Vitals: BT, BP, HR, RR)	X			X ⁷		
CBC with Hgb	X ²			X		
Coagulation tests (PT, APTT, INR)		X ⁴				
Pregnancy test (if applicable)		X ⁴				
Randomization/treatment application			X			
Assessment & determination of hemostasis at TBS			X			
Operative/surgical information			X ⁵			
Assessment of bleeding			X			
Surgeon Ease of Use Survey			X ⁶			
Adverse events			X	X	X	
Thromboembolic events possibly related or related to the TBS			X	X	X	
Postoperative re-bleeding possibly related or related to the TBS				X	X	
SAEs possibly related or related to study treatment & requiring surgical intervention			X	X	X	X ⁸

Note: Abbreviations are listed in the Glossary following these footnotes.

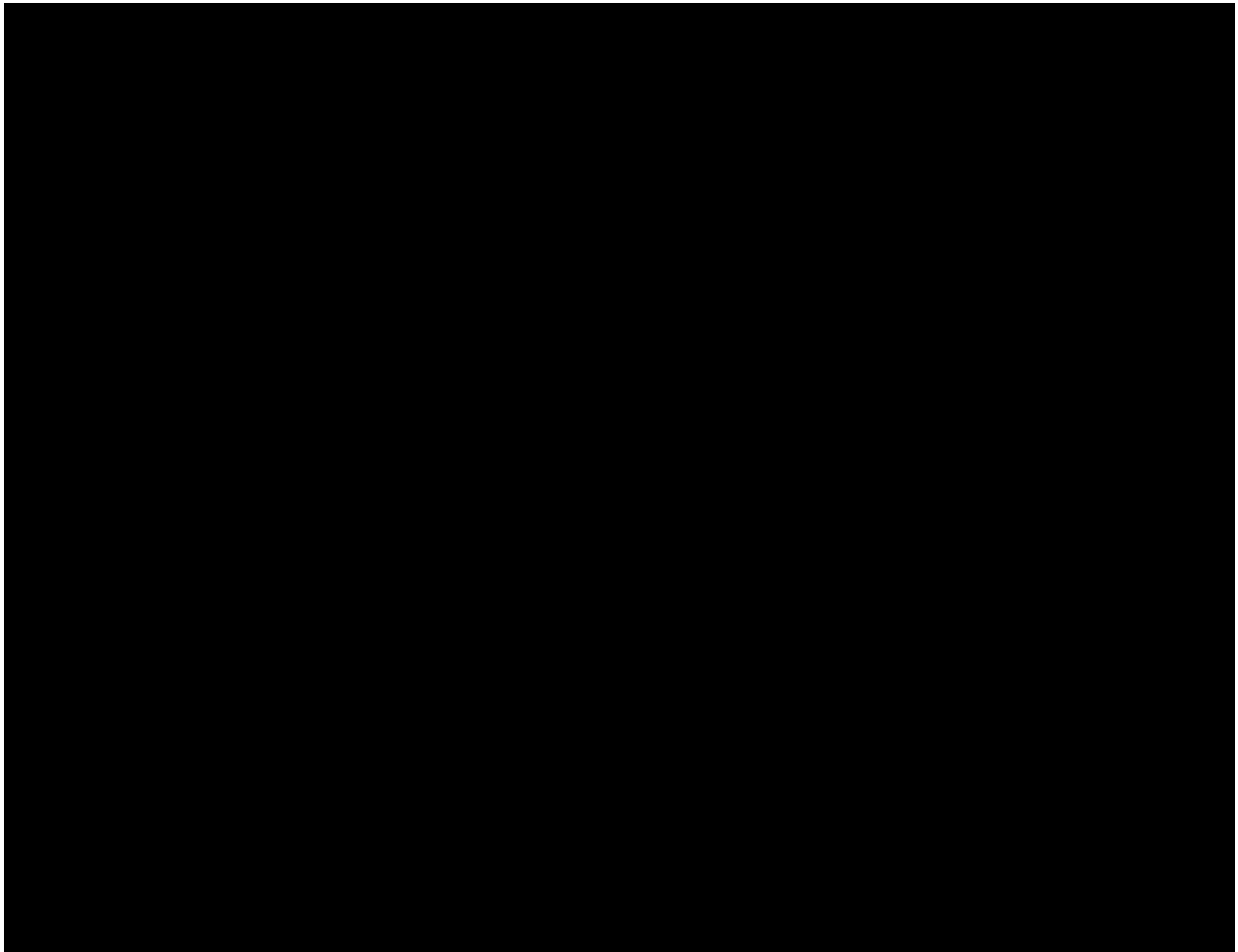
1. Screening visit may be combined with baseline visit.
2. CBC with hemoglobin blood test taken within 7 days of surgery.
3. At the baseline visit, review for changes in medical history since screening visit.
4. Blood tests to determine coagulation status, and serum or urine pregnancy test (if applicable) needed prior to 24 hours of surgery. Ensure subjects platelet count is $\geq 100,000$ per microliter and INR is < 1.5 prior to 24 hours of surgery.
5. Operative and surgical information includes EBL, transfusion information and drain information (if applicable).
6. Survey to be completed for the first 2 cases using SURGICEL Powder for each Investigator.
7. Physical exam (Vitals: BT, BP, HR, RR) performed for 3 consecutive days or up to discharge, whichever comes first.
8. New SAEs requiring surgical intervention and assessed as possibly related or related to the study treatment. All SAEs that were ongoing at the 30-day post-surgery visit will be followed until completion of the 6-month follow-up phone call or office visit, or until a stable resolution, whichever comes first.

GLOSSARY

Acronyms	Terms
ADE	Adverse Device Effect
AE	Adverse Event
AESI	adverse events of special interest
aPTT	Activated Partial Thromboplastin Time
BP	Blood Pressure
BIOS	Biosurgery
BT	Body Temperature
CBC	Complete Blood Count
CI	Confidence Interval
CTC	Common Terminology Criteria
DVT	Deep Vein Thrombosis
EBL	Estimated Blood Loss
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EUQ	Ease of Use Questionnaire
GCP	Good Clinical Practice
Hgb	Hemoglobin Blood Test
HEOR	Health Economics and Outcomes Research
HR	Heart Rate
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFU	Instructions for Use
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
J&J	Johnson & Johnson
MedDRA	Medical Dictionary for Regulatory Activities
OC	Oxidized Cellulose
ORC	Oxidized Regenerated Cellulose
OTC	Over the Counter
PE	Pulmonary Embolism
PP	Per-Protocol

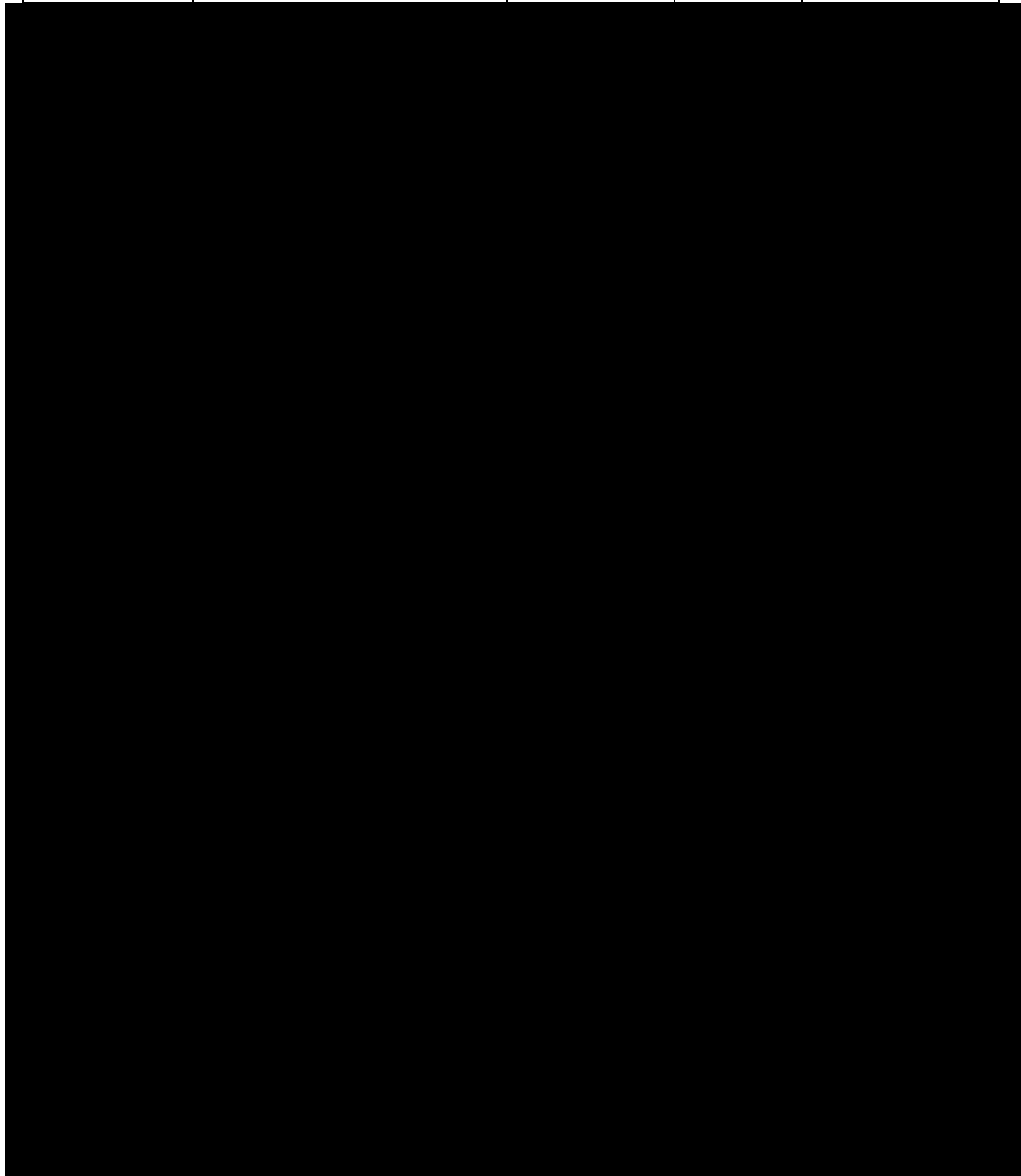
Acronyms	Terms
PSC	Product Safety Committee
PT	Prothrombin Time
RR	Respiration Rate
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMP	Safety Management Plan
SOC	Standard of Care
TBS	Target Bleeding Site
UADE	Unexpected Adverse Device Effect
USADE	Unexpected Serious Adverse Device Effect

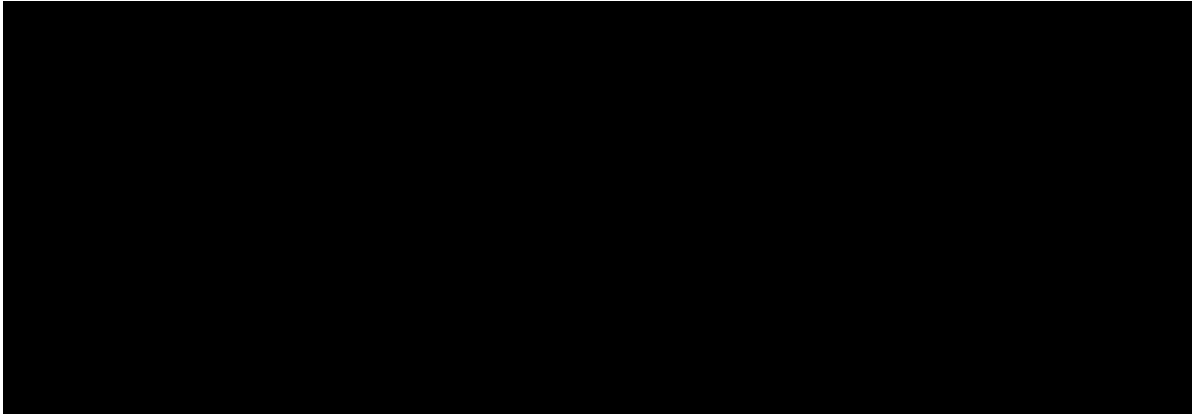
1. SPONSOR INFORMATION



2. LIST OF CLINICAL TRIAL INSTITUTIONS AND INVESTIGATORS

Code of clinical trial institution	Name of clinical trial institution	Investigator	Title	Contact
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3. OBJECTIVE AND CONTENTS OF CLINICAL TRIAL

3.1. Objective of Clinical Trial

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.

3.2. Contents of the Clinical Trial

This is a single blind, randomized, prospective study comparing SURGICEL Powder with SURGICEL Original (control) 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.

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, will be asked to provide consent by signing the ICF.

Screening and enrollment will continue until at least 234 evaluable subjects from approximately twelve (12) investigational sites, with an appropriate mild or moderate Target Bleeding Site (TBS) are randomized into the study. The TBS will be the only region evaluated for the primary endpoint and all secondary effectiveness endpoints.

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 serious adverse event (SAE) requiring surgical intervention and assessed as possibly related or related to the study treatment.

4. BACKGROUND INFORMATION OF CLINICAL TRIAL

4.1. Introduction to the Condition

4.1.1. Explanation for the Condition

Bleeding during surgical procedures may manifest in many forms and present significant perioperative morbidities¹. It may be discrete or may diffuse from a large surface area. It may be from large or small vessels; arterial (high pressure) or venous (low pressure) of

high or low volume. It may be easily accessible or it may originate from difficult to access sites. The bleeding tissues may be firm or friable. The selection of appropriate methods and products for control of bleeding is dependent on the diverse factors including bleeding intensity, anatomical location, visibility, and access to the source of bleeding.

Intraoperative and postoperative bleeding presents a substantial clinical and economic burden^{2, 3}. It may interrupt or lengthen the time of surgery and can lead to complications such as the need for transfusions and re-operations.² Overall, poor hemorrhage control is strongly linked with untoward outcomes. Adverse events related to bleeding and blood transfusion have been shown to be dose dependent, with increased transfusion rates associated with higher morbidity.⁴

The management of bleeding is critical for achieving positive outcomes for the subject, throughout the surgical procedure bleeding must be controlled in order to provide the best view of the surgical field and to prevent the adverse events associated with blood loss.⁵ Such adverse events include coagulopathy, which develops due to the body's inability to compensate for the loss of platelets and coagulation factors during emergent bleeding episodes, reduction in core body temperature, thrombocytopenia, and hypovolemic shock.⁵ In addition to the adverse events associated with blood loss, blood transfusions are associated with risks that include transfusion-associated graft-versus-host disease, administration of an incorrect blood component, hemolytic transfusion reaction, transfusion-related acute lung injury, febrile reaction, transfusion associated circulatory overload, acute respiratory distress syndrome, multiple organ failure and infections such as HIV, hepatitis A, B, and C, and malaria.⁶

If surgical hemostasis is not durable and sustained, re-operation may be necessary to find the cause of postoperative bleeding. This involves the reopening of the surgical site and the associated morbidity and mortality that accompany surgical procedures.

Effective surgical hemostasis allows fewer blood transfusions, decreased operating time, and reduced morbidity and mortality for subjects resulting in lower hospitalization costs.^{3, 5} However, primary or conventional hemostatic methods, (mechanical, thermal-based, and chemical/pharmacological) are not always sufficient or practical alone to achieve hemostasis.

4.1.2. Therapeutic Options and Prognosis

Conventional methods to achieve hemostasis include use of surgical techniques, sutures, ligatures or clips, and energy-based coagulation or cauterization.⁷ When these conventional measures are ineffective or impractical, adjunctive hemostatic techniques and products are routinely utilized to control the bleeding. Adjunctive hemostats may be

categorized into two major groups based on their mode of action: those that provide a matrix to accelerate the subject's natural coagulation cascade, and those that contain active biologic components, such as thrombin and/or fibrinogen, that will allow them to achieve hemostasis regardless of the subjects' coagulation status. The group of hemostats that assist in the coagulation cascade are also referred to as the adjunctive topical absorbable hemostats, which includes products based on oxidized cellulose (OC), oxidized regenerated cellulose (ORC), gelatin, collagen, chitin, chitosan, and polysaccharides.⁸

SURGICEL Powder and SURGICEL Original are absorbable hemostats. Both SURGICEL Powder and SURGICEL Original are indicated for use in the same subject population for adjunctive hemostasis to assist in the control of capillary, venous, and small arterial hemorrhage, when ligation or other conventional methods of control are impractical or ineffective.

With a clinical history spanning more than 50 years, SURGICEL Original and its family of products has predominately been used to assist in achieving and accelerating hemostasis, during which several types of bleeding have been observed intra-operatively. These types of products are optimal when bleeding is confined, because the product can be placed on the source of bleeding with manual compression to facilitate hemostasis. When bleeding is not confined, continuous oozing from large friable and raw surfaces can cause delays and surgeon frustration during surgery.⁹ These situations require ready to use hemostatic products with minimal or no preparation time and in addition must be able to achieve quick coverage on the bleeding surface and the ability to achieve hemostasis.

SURGICEL Powder, an optimized powdered form of ORC, is a topical absorbable hemostat being evaluated in this study to further measure its safety and hemostatic effectiveness in controlling mild to moderate parenchymal or soft tissue intra-operative bleeding. Although there is sufficient information supporting the safety and performance of SURGICEL Powder supported by data from acute and survival preclinical studies, this registration study will be implemented to further enhance our understanding of safety and performance of SURGICEL Powder in a real world clinical setting.

4.2. Application of Investigational Product

Absorbable hemostats are being increasingly used for adjunctive hemostasis to assist in the control of capillary, venous, and small arterial hemorrhage, when ligation or other conventional methods of control are impractical or ineffective. SURGICEL[®] Original is optimally applied when bleeding is confined. When bleeding is not confined, continuous oozing from large friable and raw surfaces can cause delays and surgeon frustration

during surgery. These situations require ready to use hemostatic products with minimal or no preparation time and in addition must be able to achieve quick coverage on the bleeding surface and the ability to achieve hemostasis. The SURGICEL Powder delivery device enables surgeons to topically apply a controlled quantity of powdered absorbable ORC hemostat to the desired anatomical site.

4.3. Product Registration and Reason for Clinical Trial Registration in China

SURGICEL Powder (for open procedures) received US FDA clearance on 26 May 2017 and was launched in the US market in November 2017. On June 14, 2017, SURGICEL Powder (for open and endoscopic procedures) received BSI (national standards body of the United Kingdom) approval and was added to Ethicon, LLC San Lorenzo (CE 549332) design examination certificate.

SURGICEL Powder and the SURGICEL Endoscopic Applicator have not been used in the Chinese population. Therefore, the clinical study is designed to support the registration of these devices in China.

5. EQUIVALENCE RATIONALE: SURGICEL POWDER AND SURGICEL ORIGINAL

SURGICEL Powder is manufactured directly from SURGICEL Original and measured against many of the same specifications. In a non-clinical setting, SURGICEL Powder has been shown to provide equivalent hemostasis and absorption properties, and to create a durable clot that withstands saline irrigation. It has been shown to exhibit a similar non-irritant tissue reaction, and adds no additional risk of adhesions when compared to SURGICEL Original.

SURGICEL Powder and SURGICEL Original may be considered equivalent in their technological and biological performance. Design, conditions of use, and principles of operation are the same. Materials composition is also the same and both devices have the same absorption profile (within approximately 2 weeks).

6. DESCRIPTION OF SURGICEL ORIGINAL AND SURGICEL POWDER: FEATURES, STRUCTURAL COMPOSITION, OPERATION PRINCIPLE, MECHANISM OF ACTION

SURGICEL Absorbable Hemostat (referred to as Original) has been available for more than 50 years, introduced in 1960 with a long history of safe and efficacious use. SURGICEL Original is a sterile absorbable knitted fabric produced by the controlled

oxidation of regenerated cellulose. The fabric is flexible and readily adheres to bleeding surfaces. It is a strong fabric that can be sutured or cut without fraying. SURGICEL Original is white with a pale-yellow cast and has a faint, caramel-like aroma. (Figure 1).

The entire SURGICEL family of products do not contain any medicinal substances and are derived entirely from plant materials. (The images provided in this section are for illustration purposes only and may not accurately represent the actual device.)



Figure 1: SURGICEL Original (Fabric)

SURGICEL Powder “Open-Tip” Applicator and Endoscopic Applicator

SURGICEL Powder is an absorbable hemostatic powder made of ORC. SURGICEL Powder comes in a sterile, single-use, “open-tip” applicator that dispenses the powder on a target intraoperative bleeding site during open procedures (Figure 2).

The applicator is prefilled with 3 grams of SURGICEL Powder. The “open” tip applicator enables surgeons to topically apply powder to a desired anatomical site by manually compressing the bellows of the applicator. The tip is flexible such that the surgeon can angle the tip in the direction of bleeding. The applicator is provided in the “closed” or “off” position so powder cannot be accidentally expressed prior to usage.

The mechanism of action whereby ORC hemostats accelerates clotting is believed to be a physical effect rather than any alteration of the normal physiologic clotting mechanism. After SURGICEL Powder has been saturated with blood, it swells into a brownish or black gelatinous mass that aids in the formation of a clot, thereby serving as a hemostatic adjunct.

The ORC powder is developed by producing fibrillar structured aggregates of ORC fine fibers using a proprietary process. The powder has a unique physical morphology; however, it maintains the chemical and bactericidal properties of the original ORC fabric. The ORC aggregates in SURGICEL Powder penetrate the surface layer of blood, initiating clotting and adhering to tissue for durable and sustained hemostasis. Because the ORC aggregates are chemically identical to ORC fabric products, they share key attributes and perform in ways that will be familiar to surgeons. Both induce hemostasis rapidly; turn a dark reddish-black on exposure to blood; are absorbed within

approximately 2 weeks; and, both are bactericidal in vitro for a wide range of organisms.¹⁰

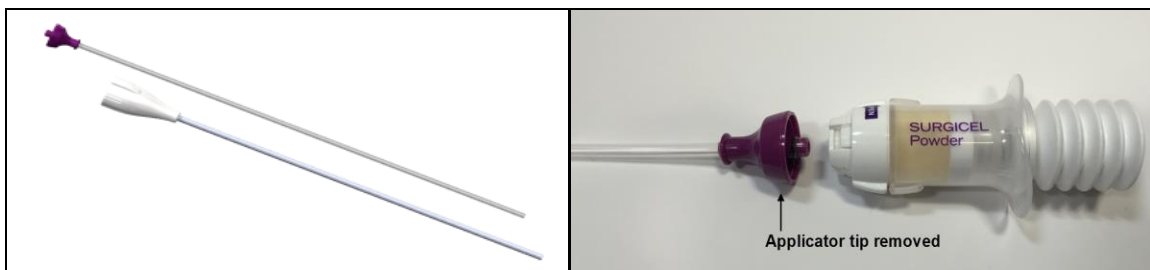


SURGICEL Powder (“Open Tip” Attached)

Figure 2: SURGICEL Powder Device

The SURGICEL Endoscopic Applicator is a Class IIa accessory device that will be packaged and sold separately for use with the SURGICEL Powder device in endoscopic/laparoscopic procedures. As shown in Figure 3, the open tip is removable and may be replaced with the SURGICEL Endoscopic Applicator (also referred to as “lap tip”).

The SURGICEL Endoscopic Applicator is supplied with a flexible inner tip and a rigid cannula and is designed to mate with the SURGICEL Powder Device, allowing for the delivery of SURGICEL Powder to a bleeding surgical site through a 5-mm or larger trocar (Figure 3).



SURGICEL Powder Endoscopic Applicator

Removal of Open Tip Applicator

Figure 3: SURGICEL Endoscopic Applicator - Interchangeable with Open Tip

6.1 Labelling and Packaging

SURGICEL Powder

The SURGICEL Powder Device will be packaged in a sealed foil laminate pouch with appropriate graphics. The material structure of the foil laminate pouch is different than the existing SURGICEL Original pouch. The existing pouch of the SURGICEL Original is paper foil laminate pouch. The SURGICEL Powder Device pouch is a poly foil laminate pouch. However, the functional barrier of both pouch materials SURGICEL Absorbable Hemostats is aluminum foil. The packaging provides protection to the devices and allows delivery of the devices into the sterile field. Ethicon assembles and packages the components with the powder to create the SURGICEL Powder Device.

Labelling may include the following:

1. Do not reuse.
2. Do not resterilize.
3. Do not use if package is damaged.
4. Caution.
5. Use-by date.
6. Temperature limit.
7. Manufacturer catalogue number.
8. Batch code.
9. Sterilized using irradiation.
10. Quantity.

SURGICEL Endoscopic Applicator

The SURGICEL Endoscopic Applicator is packaged in thermoform tray/retainer with Tyvek lid with appropriate graphics. SURGICEL Endoscopic Applicator is supplied as a disposable, sterile, single use device consisting of a flexible inner tip and a rigid cannula. SURGICEL Endoscopic Applicator is designed to mate with the SURGICEL Powder device. The SURGICEL Endoscopic Applicator consists of a rigid cannula and a flexible elongated tube with connectors to attach to the auxiliary device (SURGICEL Powder Device), allowing for delivery of powdered hemostat in endoscopic procedures by compression of the SURGICEL Powder Device bellows. The SURGICEL Endoscopic Applicator is disposable and must be discarded after use.

6.2 Shipping, Handling and Storage Conditions

Store unopened packages of SURGICEL Powder at 15° to 30 °C. SURGICEL Powder does not require refrigeration. Do not freeze. Do not use if package is opened or damaged. Sterility is guaranteed unless package is opened or damaged.

The applicator is provided sterile with 3 grams of SURGICEL Powder (ORC) and should not be re-sterilized/reused. Do not re-sterilize/reuse SURGICEL Powder or the SURGICEL endoscopic tip. Once opened, keep dry prior to use, so that it can remain in the sterile field throughout the surgery. Disposal of the device, the endoscopic tip (if used for appropriate surgery), and packaging will be in accordance with study facility policies and procedures regarding biohazardous materials and waste.

Distribution of SURGICEL Powder and the endoscopic accessory to the clinical sites will be performed by a qualified distribution center with proper inventory and quality control capabilities once all the necessary documentation and approvals are obtained.

7. LITERATURE REVIEW

To date, there have been no clinical investigations conducted on SURGICEL Powder, therefore the body of evidence for the safety and effectiveness of Surgical Powder is based on published clinical data on the equivalent comparator, SURGICEL Original. The equivalence rationales between the equivalent comparator hemostat, SURGICEL Original and its “open tip” applicator, with the subject device, SURGICEL Powder and the SURGICEL Endoscopic Applicator accessory (“lap tip”) are duly justified regarding clinical, technical, and biological characteristics with no impact on clinical safety and performance outcomes.

The reviewed literature covered all published on-label SURGICEL Original articles from 01 January 1998 to 10 October 2017, and included 33 studies with 33,249 subjects. The effectiveness of SURGICEL in achieving hemostasis was evaluated in a variety of open, laparoscopic, and other minimally invasive surgical approaches, and the included study populations were representative of the target population in terms of demographics and device use. Clinical data from the included studies demonstrated the acceptable performance and safety of SURGICEL when used as intended, relative to the state of the art. Re-bleeding at the site of SURGICEL placement was reported in 17 included studies for an overall median of the means of 6.6% of subjects experiencing re-bleeding after application of SURGICEL. None of the deaths that occurred were reported as related to the use of SURGICEL, and the reported complications were not described as attributable to the use of SURGICEL by the authors. In conclusion, clinical data from the included studies demonstrate the acceptable performance and safety of SURGICEL when used as intended, relative to the state of the art.

The available non-clinical dataset further substantiates SURGICEL Powder and accessory, SURGICEL Endoscopic Applicator, as state-of-the-art medical device for use as an adjunctive hemostat delivered to the target bleeding site.

Literature supporting performance of SURGICEL Powder (85%) versus SURGICEL Original (80%) for the 5-minute primary endpoint.

The 80% success rate assumption for the primary effectiveness endpoint in the SURGICEL Original group is supported by the following clinical investigations.

Fischer 2013 treated 30 patients with SURGICEL and 60 patients with fibrin pad in nonemergent surgery where the site of bleeding was in the retroperitoneal, thoracic, pelvic, and abdominal regions. Surgery was performed according to the standard of care, except other fibrin sealants or topical thrombin were not permitted. Among patients with mild bleeding, 80% who received SURGICEL Original had achieved hemostasis at 4 minutes.

Genyk 2016 compared SURGICEL Original (110 patients) versus TachoSil (114 patients) in laparoscopic and open hepatic resection; 76.4% of patients who received SURGICEL Original achieved hemostasis at 5 minutes.

Li H. 2017 compared SURGICEL Original (108 patients) versus Fibrin Sealant (116 patients) during soft tissue open surgeries; 78% of patients who received SURGICEL Original achieved hemostasis at the primary endpoint of 4 minutes. A similar study supported by Grifols, was also performed comparing SURGICEL Original (113 patients) versus Fibrin Sealant (111 patients) during parenchymous tissue open surgeries; 81% of patients who received SURGICEL Original achieved hemostasis at the primary endpoint of 4 minutes.

To date, there have been no clinical investigations conducted on SURGICEL Powder. The 85% success rate assumption for the primary effectiveness endpoint for SURGICEL Powder in this proposed randomized clinical trial is supported by the following preclinical studies.

Pivotal Study Comparing Performance of Surgicel Powder-Absorbable Hemostatic Powder to SURGICEL Original Absorbable Hemostat in a Swine Acute Liver Abrasion Model. A 256-mg application of SURGICEL Powder had a median TTH of 222 seconds, while the mass equivalent application of SURGICEL Original (2-layer equivalent) had a median TTH of 407 seconds. Therefore, the SURGICEL Powder TTH was 47% faster than the TTH for the mass equivalent application of SURGICEL Original. A 384-mg application of SURGICEL Powder had a median TTH of 173 seconds, while the mass equivalent application of SURGICEL Original (3-layer equivalent) had a median TTH of 357 seconds. Therefore, the SURGICEL Powder TTH was 52% faster than the TTH for the mass equivalent application of SURGICEL Original. In conclusion, the study confirmed that SURGICEL Powder provided equivalent hemostatic performance within the pre-set 10-minute period, and a faster TTH (see Section 8).

Porcine Study on Mass of SURGICEL Powder Compared to Mass of Currently Marketed Topical Powdered Hemostats. This study was conducted to compare two different masses of SURGICEL Powder with two equivalent masses of currently marketed topical powdered hemostats. SURGICEL Powder had 93% and 89% faster median TTH values than the other topical hemostats. Furthermore, SURGICEL Powder TTH values for individual test sites were all 3 minutes or less (median: 30 seconds), while the comparators both had sites with TTH values of 10 minutes or greater recorded (median values of 285.5 seconds and 423 seconds, respectively). (See Section 8).

In this clinical RCT, the primary endpoint is hemostasis at 5 minutes, while in the preclinical studies summarized above, the median TTH for SURGICEL Powder was less than 4 minutes.

Therefore, it is reasonable to assume a 5% higher success rate for hemostasis at 5 minutes with SURGICEL Powder (85%) when compared to SURGICEL Original (80%).

8. PRECLINICAL TESTING

Efficacy of SURGICEL Powder was demonstrated in four animal studies. The first of the nonclinical efficacy studies was an acute evaluation performed in pigs and the second was a survival model in rats. Both studies compared the performance (efficacy) of SURGICEL Powder with that of SURGICEL Original. The rat study was also conducted for biocompatibility evaluation. A third study was performed in pigs to evaluate the acute hemostatic efficacy of SURGICEL Powder when compared with two currently marketed topical powdered hemostats. The fourth study was conducted in pigs to compare performance of SURGICEL Powder with SURGICEL Original using a liver abrasion defect in a 2-day and 21-day recovery model. These studies are summarized below.

Study 1: Pivotal Study Comparing Performance of Surgicel Powder-Absorbable Hemostatic Powder to Surgicel Original Absorbable Hemostat in a Swine Acute Liver Abrasion Model¹¹

A pivotal nonclinical laboratory study was conducted to evaluate the performance of Surgicel Powder compared with that of the equivalent, Surgicel Original, in a diffuse area, mild bleeding, porcine liver abrasion model. The primary objective of this study was to determine whether Surgicel Powder was as effective as an equivalent mass of Surgicel Original for achieving hemostasis in a standardized (3 cm x 3 cm) liver abrasion defect. The secondary objective was to evaluate persistence of the powdered product and durability of hemostasis in this model by determining whether Surgicel Powder remained Hemostatic after saline irrigation once hemostasis was achieved at a bleeding defect site. The study was also designed to determine the time to hemostasis (TTH) for two different

mass equivalent applications of the test article and equivalent device. During this study, five test animals underwent 10 liver abrasions 3 cm by 3 cm in size, allowing for a combined total of 50 control, test and equivalent evaluations across five animals.

Hemostatic Efficacy

The study confirmed that when applied to swine liver abrasion defects at 256 mg and 384 mg mass applications, SURGICEL Powder was effective at controlling hemorrhage within 10 minutes of initial application at 100% of defect sites. The study also confirmed that the hemostatic efficacy of an equivalent mass of SURGICEL Powder and SURGICEL Original were not statistically different.

Durable Hemostasis (lack of re-bleeding)

The study demonstrated that SURGICEL Powder applications that were effectively hemostatic remained hemostatic following saline lavage at 90% of defect sites tested (i.e., there was no re-bleeding at the sites following saline lavage). Additionally, the study acceptance criterion of remaining hemostatic at the majority (>50%) of sites after saline irrigation was exceeded for both mass applications of SURGICEL Powder.

Time to Hemostasis (TTH)

A 256-mg application of SURGICEL Powder had a median TTH of 222 seconds, while the mass equivalent application of SURGICEL Original (2-layer equivalent) had a median TTH of 407 seconds. Therefore, the SURGICEL Powder TTH was 47% faster than the TTH for the mass equivalent application of SURGICEL Original. A 384-mg application of SURGICEL Powder had a median TTH of 173 seconds, while the mass equivalent application of SURGICEL Original (3-layer equivalent) had a median TTH of 357 seconds. Therefore, the SURGICEL Powder TTH was 52% faster than the TTH for the mass equivalent application of SURGICEL Original. In conclusion, the study confirmed that SURGICEL Powder provided equivalent hemostatic performance within the pre-set 10-minute period, and a faster TTH.

Study 2: ISO Systemic Toxicity Study of SURGICEL POWDER in a Multi-Organ Implantation Model in Rats- 1, 2, and 3 Weeks

The purpose of this study was to evaluate the biocompatibility of SURGICEL Powder and also the TTH in this rat model. The total article dose was distributed over a total of four sites: one liver defect, one spleen defect, one subgluteal (intermuscular), and one subcutaneous site. The first two sites included an assessment of hemostasis efficacy and the second two sites did not include bleeding. Results were compared with a marketed device, SURGICEL Original Hemostat, which served as the control article. In the liver

sites, the TTH was 318 \pm 8 and 322 \pm 23 seconds for the test and control groups respectively. In the spleen sites, the TTH was 334 \pm 59 and 337 \pm 83 seconds for the test and control groups, respectively. There were no statistically significant differences between test and control groups.

Study 3: Porcine Study on Mass of SURGICEL Powder Compared to Mass of Currently Marketed Topical Powdered Hemostats¹²

This study was conducted to compare two different masses of SURGICEL Powder with two equivalent masses of currently marketed topical powdered hemostats. The hemostatic efficacy and TTH within ≤ 10 minutes in a standardized (6 mm diameter x 3 mm depth) swine liver punch biopsy defect were evaluated and compared for all 3 powdered products. Additionally, the persistence of the powdered products and durability of intraoperative hemostasis were evaluated and compared by determining the products ability to remain Hemostatic following saline irrigation once hemostasis was achieved at the bleeding site.

In the study, fourteen standardized liver punch biopsy defects, with mild or moderate bleeding, were created and treated in each of 5 pigs, allowing for a combined total of 70 control, test, and comparator evaluations across the five animals. Doses of 125 mg and 75 mg were evaluated. For each animal, the first and last defect sites created served as negative controls treated with tamponade alone. The testing order for the remaining 12 sites were randomized within each animal.

SURGICEL Powder had 93% and 89% faster median TTH values than the other topical hemostats. Furthermore, SURGICEL Powder TTH values for individual test sites were all 3 minutes or less (median: 30 seconds), while the comparators both had sites with TTH values of 10 minutes or greater recorded (median values of 285.5 seconds and 423 seconds respectively). Once hemostasis was achieved, 90% of SURGICEL Powder sites remained Hemostatic after saline irrigation.

Study 4: Efficacy and Safety Evaluation of SURGICEL Powder Absorbable Hemostatic Powder in Swine – 2 Days and 21 Days¹³

This porcine study evaluated the Hemostatic efficacy and safety of SURGICEL Powder Absorbable Hemostatic Powder (test article) by evaluating intraoperative as well as sustained postoperative hemostasis when SURGICEL Powder was used to control bleeding at sites of tissue abrasion through 21 days. In addition, local tissue response to the test article was evaluated; device migration was investigated and the incidence and severity of adhesion formation was documented. The study also examined the local tissue

response as well as distal tissue response that result from device associated thrombotic events and particle embolization. Results for the test article were compared to those for SURGICEL Original Absorbable Hemostat (control article).

Abrasion defects measuring approximately 3 cm x 3 cm were created on the diaphragmatic and visceral surfaces of two or more separate liver lobes of 24 farm pigs (a total of four abrasion defects per animal). The defect areas were abraded until capillary, venous and/or small arterial hemorrhage occurred. In 12 animals, the test article was applied to all four defect sites (test article treatment group). The control article was applied to all four defects in the remaining 12 animals (control article treatment group). Once all defects were treated and hemostasis was achieved, the animals were closed in a standard fashion and recovered from anesthesia. Periodic assessments for general health, mucous membrane color, and body weight were conducted. At 2 and 21 days, six animals from the test treatment group and six animals from the control treatment group were euthanized. A gross necropsy was performed and assessments made for, but not limited to: evidence of free blood within the abdominal cavity, evidence of bleeding or hematoma formation at the defect sites, incidence and severity of adhesion formation, article migration and device associated distal thrombosis or particle embolization. Tissue sections from the liver defect sites, adjacent liver parenchyma, abdominal and thoracic lymph nodes, major hepatic blood vessels and vena cava, kidneys, spleen and a representative section from each lung lobe were collected, fixed, histologically processed, and microscopically evaluated. In addition, representative tissue sections were collected as warranted from any macroscopic alterations noted at necropsy.

No early deaths were seen during this study. All test and control article treatment sites were effectively Hemostatic intraoperatively and sustained hemostasis postoperatively with no statistical differences present. At 2 and 21 days, gross necropsy findings were similar with no statistical difference between test and control animals for: adhesion incidence or severity at defect sites, article embolization (none present), hematoma at defect sites (none detected macroscopically), and re-bleeding (none present). For article migration/adhesion, suspect migration was noted macroscopically at 3/24 test sites at 2 days; however, migration from these sites was not confirmed microscopically. Necropsy findings for lung lesions were present in two control (21 days) animals and one test (2 days) animal. Findings were not attributed to treatment with the articles but were consistent with aspiration or bronchopneumonia.

Microscopically, the test article was considered a non-irritant to the tissue at 2 and 21 days following surgery as compared to the control article. The type and amount of inflammation and adhesions observed at 2 and 21 days post-operatively was consistent between test and control groups. There were no microscopically evident areas of

thrombosis or embolization and no test article was identified at defect sites or presumed sites of article migration. The test article provided excellent Hemostatic performance and had similar tissue response and similar adhesion incidence and severity as the control article, and had no detected adverse systemic effects (no thrombosis or particle embolization).

8.1. Comparison with Other Hemostatic Powders

SURGICEL Powder was compared with other commercially available hemostatic powder products in two in vivo models. Hemostatic efficacy of SURGICEL Powder was compared with two polysaccharide-based hemostats in a porcine liver punch biopsy model and with three polysaccharide-based hemostats and one non-regenerated oxidized cellulose hemostat in a porcine liver abrasion model. SURGICEL Powder provided more effective hemostasis (defined as hemostasis within 10 minutes of application), and faster time-to-hemostasis TTH than the other marketed hemostatic powders. The results from this in vivo study suggest that SURGICEL Powder may be useful in clinical applications where control of oozing capillary, mild venous, and small arterial hemorrhage is required, including bleeding in difficult-to-access locations.

9. INDICATIONS AND CONTRAINDICATIONS, PRECAUTIONS

9.1. Indication

SURGICEL Powder is used adjunctively in surgical procedures to assist in the control of capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective.

9.2. Contraindications

All hazards associated with the use of SURGICEL Powder have been identified and appropriately mitigated.

This product should only be used by clinicians and staff properly trained in the use of the technology and its associated warnings and cautions.

SURGICEL Powder:

- Do not inject or place SURGICEL Powder into an open blood vessel. Do not use to treat bleeding from large defects in arteries or veins.
- SURGICEL Powder should not be used to control hemorrhage from large arteries or veins.

- The SURGICEL Powder device was not designed for intraluminal procedures.
- When SURGICEL Powder is used to help achieve hemostasis in, around, or in proximity to foramina in bone, areas of bony confine, the spinal cord, or the optic nerve and chiasm, it must always be removed after hemostasis is achieved since it will swell and could exert unwanted pressure. Unlike other SURGICEL products, SURGICEL Powder cannot be removed from blood clots and complete removal of the device application may disrupt the clot and increase the risk of re-bleeding.
- SURGICEL Powder should not be used for implantation in bone defects, such as fractures, since there is a possibility of interference with callus formation and a theoretical chance of cyst formation.
- SURGICEL Powder should not be used on non-hemorrhagic serous oozing surfaces, since body fluids other than whole blood, such as serum, do not react with SURGICEL Powder to produce satisfactory hemostatic effect.
- SURGICEL Powder is an absorbable hemostat, and should not be used as an adhesion prevention product.

SURGICEL Endoscopic Applicator

- Do not inject or place SURGICEL Powder into an open blood vessel. Do not use to treat bleeding from large defects in arteries or veins.
- SURGICEL Powder should not be used to control hemorrhage from large arteries or veins.
- The SURGICEL Endoscopic Applicator was not designed for intraluminal procedures.

9.3. Warnings and Precautions

- SURGICEL Powder is not intended for use on dry (non-bleeding) surfaces or for prevention of bleeding.
- SURGICEL Powder is supplied sterile and as the material is not compatible with autoclaving or ethylene oxide sterilization, SURGICEL Powder should not be resterilized.
- SURGICEL Powder is not intended as a substitute for careful surgery and the proper use of sutures and ligatures.
- Closing with SURGICEL Powder in a contaminated wound without drainage may lead to complications and should be avoided.

- The hemostatic effect of SURGICEL Powder is greater when it is applied dry; therefore, it should not be moistened with water or saline prior to application.
- SURGICEL Powder should not be impregnated with anti-infective agents or with other materials such as buffering or hemostatic substances. Its hemostatic effect is not enhanced by the addition of thrombin, the activity of which is destroyed by the low pH of the product.
- Although SURGICEL Powder may be left in situ when necessary, it is recommended to remove excess powder with irrigation and aspiration once hemostasis is achieved, without disturbing the clot.
- SURGICEL Powder is dry and there may be difficulties in precise delivery under certain circumstances. Unintentional device placement may result in powder scattering and device migration that may increase the risk of adhesion formation. In preclinical in vivo animal studies it was demonstrated that SURGICEL Powder does not increase the incidence of remote adhesions in laparoscopic procedures.
- Dislodgement of SURGICEL Powder could possibly occur by intraoperative manipulation, lavage, exaggerated respiration, etc. With other SURGICEL products, there have been reports that in procedures such as lobectomy, laminectomy, and repair of a frontal skull fracture and lacerated lobe, when the product was left in the subject after closure it migrated from the site of application into foramina in bone around the spinal cord, resulting in paralysis and, in one case, the product migrated into the left orbit of the eye, causing blindness. While these reports cannot be confirmed to be related to SURGICEL products, special care must be taken by physicians, regardless of the type of surgical procedure. Consider removing SURGICEL Powder in these applications (procedures) after hemostasis is achieved.
- Although SURGICEL Powder is bactericidal against a wide range of pathogenic microorganisms, it is not intended as a substitute for systemically administered therapeutic or prophylactic antimicrobial agents to control or to prevent postoperative infections.
- Do not resterilize/reuse. Reuse of this device (or portions of this device) may create a risk of product degradation, which may result in device failure and/or cross-contamination, which may lead to infection or transmission of blood-borne pathogens to patients and users.
- Do not attempt to trim the applicator tip.

- SURGICEL Powder should not be used in conjunction with autologous blood salvage circuits, because its fragments may pass through the transfusion filters of blood-scavenging systems.
- Use only as much SURGICEL Powder (oxidized regenerated cellulose) as is necessary and apply only where needed for hemostasis. Remove any excess before surgical closure in order to facilitate absorption and to minimize the possibility of foreign body reaction.
- Use minimal amount of SURGICEL Powder required to achieve hemostasis, and remove excess powder in the area of drains to prevent clogging. In urological procedures, minimal amounts of SURGICEL Powder should be used and care must be exercised to prevent plugging of the urethra, ureter, or a catheter by dislodged portions of the product.
- Since absorption of SURGICEL Powder could be prevented in chemically cauterized areas, its use should not be preceded by application of silver nitrate or any other escharotic chemicals.
- If SURGICEL Powder is used temporarily to line the cavity of open wounds, it should be removed by irrigation with sterile water or saline solution after bleeding has stopped.
- Precautions should be taken in otorhinolaryngologic surgery to ensure that none of the material is aspirated by the subject (e.g., controlling hemorrhage after tonsillectomy and controlling epistaxis).
- The applicator tip provided on the SURGICEL Powder device is not intended for laparoscopic or other endoscopic use. If laparoscopic or other endoscopic use is desired, remove the existing applicator tip from the SURGICEL Powder device, and replace with the SURGICEL Endoscopic Applicator tip (supplied separately). In laparoscopic or other endoscopic procedures, SURGICEL Powder should only be applied using the SURGICEL Endoscopic Applicator. Consult the SURGICEL Endoscopic Applicator Instructions for Use (IFU) for proper assembly and directions for use with the SURGICEL Powder device.

SURGICEL Endoscopic Applicator

- The SURGICEL Endoscopic Applicator is supplied sterile and as the material is not compatible with autoclaving or ethylene oxide sterilization, the SURGICEL Endoscopic Applicator should not be resterilized.
- To prevent clogging, do not touch the tip to wet surface. Be careful to avoid damaging tissue with the rigid tip.

- Do not attempt to trim the applicator tip. Replace the tip if it becomes clogged.
- Do not use the SURGICEL Endoscopic Applicator if package is opened or damaged.
- Apply SURGICEL Powder according to the product's labeling.
- Do not resterilize/reuse. Reuse of this device (or portions of this device) may create a risk of product degradation, which may result in device failure and/or cross-contamination, which may lead to infection or transmission of blood-borne pathogens to patients and users.
- The SURGICEL Endoscopic Applicator is supplied with a flexible inner tip inside a rigid cannula. The rigid cannula cannot be used independently.
- The SURGICEL Endoscopic Applicator should only be used by persons having adequate training and familiarity with endoscopic techniques. Consult medical literature relative to techniques, complications, and hazards prior to performance of any endoscopic procedure.
- After use, dispose of the SURGICEL Endoscopic Applicator in accordance with biohazardous material protocol.

10. OVERALL DESIGN

10.1. Trial Design

This is a single blind, prospective, randomized, multicenter, multispecialty, controlled clinical study comparing SURGICEL Powder with SURGICEL Original 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 (≥ 18 years old) subjects.

At least 234 evaluable subjects with an appropriate mild or moderate TBS will be randomized in a 1:1 allocation ratio to either SURGICEL Powder or SURGICEL Original (control).

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 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 or related to the study treatment.

10.1.1. Trial Objective

The objectives of this 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 of Chinese adult (≥ 18 years old) subjects.

10.1.2. Trial Method Selection and Its Rationale

This is a single blind, prospective, randomized, controlled clinical study. 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, will be asked to provide consent by signing the ICF.

The Investigator is expected to invite all subjects expected to meet the study entry criteria to participate in the study.

10.1.3. Measures to Reduce and Avoid Bias

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 evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

The study related data will be recorded in the original Medical Records and reviewed during the monitoring process. Proper training for the investigators will be planned to ensure all investigators have equal and adequate experience with the device prior to commencing enrollment at their site.

10.1.4. Trial Endpoints

Primary Effectiveness Endpoint

- 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.

Secondary Effectiveness Endpoints

- 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.

Safety Endpoints

- Incidence of thromboembolic events that were assessed as possibly 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 or related to the TBS 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 or related to the study treatment (from enrollment through the 6-month follow-up phone call or office visit)

10.1.5. Study Entry Criteria

Inclusion criteria

Pre-operative:

1. Adult subjects ≥ 18 years requiring elective/non-emergent open or laparoscopic general, gynecological, or cardiothoracic surgical procedures;
2. Subject or authorized representative has signed the approved Informed Consent;
3. Subject(s) whose platelet count is $\geq 100,000$ per microliter and International Normalized Ratio (INR) is < 1.5 prior to 24 hours of surgery.

Intra-operative:

4. Presence of an appropriate TBS identified intra-operatively by the surgeon;
5. Subject(s) undergoing cardiothoracic surgery with anticoagulation must have anticoagulation reversed prior to TBS identification and treatment.

Exclusion criteria

Pre-operative:

1. Female subjects who are pregnant or nursing.
2. Subject on heparin within 12 hours prior to surgery, or oral Coumadin (warfarin) and/or Factor Xa inhibitors within 3 days prior to surgery.
3. Subject on antiplatelet/P2Y12 inhibitors medication within 5 days prior to surgery.
4. Subject is currently participating or plans to participate in any other investigational device or drug trial without prior approval from the Sponsor.
5. Subjects who are known, current alcohol and/or drug abusers.
6. Subjects with any pre-operative findings identified by the surgeon that may preclude conduct of the study procedure.

Intra-operative:

7. Subjects with any intra-operative findings identified by the surgeon that may preclude the use of study product.
8. Subject with TBS in an actively infected field (Class III Contaminated or Class IV Dirty or Infected; see Appendix 1).
9. TBS is on arteries or veins where application of SURGICEL Powder would present a risk of introducing the study product into an open blood vessel.
10. Major arterial or venous bleeding or major defects in arteries and veins.
11. TBS where silver nitrate or any other escharotic chemicals have been applied.
12. TBS is in, around, or in proximity to foramina in bone, or areas of bony confine, the spinal cord, or optic nerve and chiasm.

10.1.6. Criteria of Sponsor's Discontinuation of the Trial

Both the Investigator and Ethicon reserve the right to terminate the study at any time. Should this be necessary, the procedures will be arranged on an individual study basis after review and consultation with both parties. In terminating the study, Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests and safety.

The Sponsor has the right to terminate the study early for a single site, multiple sites or all sites temporarily or permanently. Reasons may include, but are not limited to: safety issue or ethical issue, inaccurate or incomplete data record, non-compliance or dissatisfactory quality or quantity of the recruited subjects. Health authorities also have the right to terminate a study.

The Sponsor's Medical Director (Study Medical Monitor/Safety Lead) will assess all SAEs for causality and expectedness and will utilize Ethicon's Product Safety Committee (PSC) to review and adjudicate the following safety signals:

- Thromboembolic events
- Postoperative re-bleeding
- Reoperations for complications assessed as possibly related or related 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 also give a final assessment of the safety of the product from this study. The composition, responsibilities, frequency of PSC meetings, handling of emergency situations, and documentation of PSC meetings will be specified in the Safety Management Plan (SMP).

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 SAEs (pulmonary embolism [PE] / deep vein thrombosis [DVT]) are reported and assessed as being related to SURGICEL Powder
- If one or more subjects develop post-operative bleeding and the TBS is confirmed as the cause of the re-bleeding. The relatedness of the SAE to SURGICEL Powder is to be determined by the following:
 - Findings at re-operation
 - Findings of TBS re-bleeding at autopsy (if applicable).

Flow of Sponsor's Discontinuation of the Trial:

If this study is terminated or discontinued early, the Sponsor or its representative will inform the Investigator/affiliated unit and regulatory authority of the termination of the study and the reasons for the termination or discontinuation, according to the applicable requirements. The Sponsor or Investigator/affiliated unit should also inform ECs and include the reasons for termination or discontinuation, according to the applicable requirements. In addition, all unused study products and other study materials should be returned according to the Sponsor's study procedures.

Study/Treatment Termination and Subject Discontinuation Criteria and Procedures

In accordance with the current revision of the Declaration of Helsinki, a subject has the right to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or the institution. Should a subject (or subject's legally authorized guardian/representative) decide to withdraw, 1) all data collected up to the point of withdrawal will be considered for analysis; and 2) all efforts will be made to collect and report the final visit observations as thoroughly and timely as possible. The primary reason for early withdrawal will be recorded on the electronic case report form (eCRF). The criteria for withdrawal of subjects from the study include, but are not limited to, the following:

Withdrawal of consent: Any method of contact with the subject in which the subject's states that he or she no longer wants to participate in the study-specific activities constitutes withdrawal of consent from participation in the study. This decision must be "self-determination" and should be documented in the eCRF; or, the Investigator may determine the withdrawal of subjects from the study according to reasonable medical judgement;

Adverse event: The AE or SAE may not cause the subjects to discontinue the study treatment. If the Investigator decides to withdraw a subject from the study, this subject must be followed up, until the AE is resolved or until the stable clinical endpoint is reached;

Death: The cause of death will be documented.

Lost-to-follow-up: All subjects should be able to participate in all scheduled clinical follow-ups, providing the appropriate contact information. If a subject can't return to undergo the scheduled clinical visit, attempts to contact the subject by phone should be done for 3 times to ask the subject to participate in all scheduled clinical follow-ups. Each attempt to contact should be recorded in the source document. If the subject makes no response to all three times of telephone contact, the Investigator must send a registered mail to the subject. If the subject makes no response to the registered mail and makes no further contact, the subject is considered lost-to-follow-up and the respective eCRF will be completed.

10.1.7. Procedure for Subject's Discontinuation from Study Treatment

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 or related to the study treatment.

If the subject is withdrawn from the study early, the reasons for termination will be

documented in the source document and site files, and submitted via the eCRF.

The subjects withdrawn from the study early will be included in the analysis of results; however, no new subjects will be recruited to replace the subjects withdrawn from the study, as a 10% attrition rate has already been taken into account in the current sample size.

10.1.8. Enrollment

Subjects will be considered enrolled into the study upon satisfaction of the following criteria:

- Completion of the informed consent process.
- It is determined by the Investigator that the subject meets all inclusion criteria and does not meet any exclusion criteria.

No procedures related to the study and which are not SOC should be conducted prior to signing the informed consent.

10.1.9. Expected overall duration of clinical trial and reasons for determination

The expected overall duration is approximately 30 months, including the time that each site's Ethics Committee takes to approve the trial protocol, institution contract sign-off, Human Genetic Resources Office approval, duration of subject enrollment, duration of follow-up, time for data management, statistical analysis, and time to write, review and approve the clinical study report.

10.1.10. Expected duration of participation of each subject

The duration of each subject's participation in the study will be around 6 to 7 months (about 3 weeks for Screening and 6 months for follow-up).

10.1.11. Number of subjects required for clinical trial

At least 210 evaluable subjects (105 per treatment group) are required for this study. To account for a 10% drop-out rate, a total of 234 randomized subjects (117 per treatment arm) will be randomized. See Section 13.3 Calculation of Sample Size for the basis for selecting this sample size.

10.1.12. Effectiveness Evaluation Method

Description of Effectiveness parameters

The primary efficacy endpoint is:

- 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.

The secondary efficacy endpoints are:

- 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 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.

Selection of method and time to evaluate, record and analyze the efficacy parameters

The primary effective parameter in this study will be assessed by the Investigator(s) at each site based on hemostatic success at 5 minutes intra-operatively. The secondary effective parameters in this study will be assessed by the Investigator(s) at each site based on hemostatic success at 3 and 10 minutes intra-operatively. The statistical analyses performed for the effectiveness endpoints are presented in Section 13.2.

10.1.13. Safety Evaluation Method

Description of safety parameters

The safety parameters in this study are the following:

- Incidence of thromboembolic events that were assessed as possibly 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 or related to the TBS and requiring medical/surgical intervention (from initiation of final fascial closure through the 30-day follow-up phone call or office visit);
- Incidence of serious adverse events requiring surgical intervention and assessed as possibly related or related to the study treatment (from enrollment through the 6-month follow-up phone call or office visit)

Selection of method and time to evaluate, record, and analyze the safety parameters

Subjects will be assessed for all AEs and SAEs from time of ICF through the 30-day follow-up. At the 6-month follow-up, only SAEs requiring surgical intervention and assessed as possibly related or related to the study treatment, will be reported. The safety

parameters are recorded on the e-CRF according to the Investigator's record, medical record, and all other related source documents, which are collected at each follow-up visit.

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

- Thromboembolic events
- Postoperative re-bleeding
- Reoperations for complications assessed as possibly related or related 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 also give a final assessment of the safety of the product from this study. The composition, responsibilities, frequency of PSC meetings, handling of emergency situations, and documentation of PSC meetings will be specified in the Safety Management Plan (SMP).

10.2. Standard Operating Procedures of Medical Product

10.2.1. Indication and scope of application

SURGICEL Powder, Absorbable Hemostatic Powder (oxidized regenerated cellulose) is used adjunctively in surgical procedures to assist in the control of capillary, venous, and small arterial hemorrhage when ligation or other conventional methods of control are impractical or ineffective.

Surgical procedures within the scope of this protocol are single blinded, laparoscopic, or thoracoscopic surgical procedures with a mild or moderate parenchyma or soft tissue identifiable TBS.

Surgical procedures may include the following:

- General
- Gynecological
- Cardiothoracic.

10.2.2. Warnings and precautions

All hazards associated with the use of the Surgicel Powder are listed in sections 9.2 and 9.3 as well as in the IFU and IB.

This product should only be used by clinicians and staff properly trained in the use of the technology and its associated warnings and cautions.

Refer to the Surgicel Powder accompanying documents for a complete and comprehensive list of Warnings and Cautions.

11. STUDY PROCEDURES AND EVALUATIONS

Refer to Table 1: Schedule of Activities, which may be found at the end of the Protocol Summary.

11.1. Screening

Subjects will be consented prior to any actual study-specific screening procedures being conducted. Subjects will be considered enrolled into the study upon satisfaction of the following criteria:

- Completion of the informed consent process and signing the Informed Consent Form (ICF).
- Verification of the eligibility criteria by the Principal Investigator (PI) and/or authorized investigators. The verification must be conducted by the PI and/or authorized investigators prior to performing any study-related procedure or completing any form associated with this study.
- Identification of an appropriate mild or moderate TBS intra-operatively where the subject is randomized.

11.1.1. Screen Failures

Screened subjects who are not enrolled will be considered screen failures. For subjects who are determined to be screen failures, only the following data will be recorded on the eCRF:

- Informed consent date.
- Demographic information (age, race, gender, and ethnicity).
- Reason for screening failure.

11.1.2. Screening (Within 21 Days Prior to Surgical Procedure)

Prospective subjects will be screened within 21 days prior to surgery. The following activities and tests will be performed at the Screening visit. The timing of these activities may occur based on routine hospital practice but may be done up to the day of, but prior to, the surgical procedure:

- The subject must be given ample time to review and sign the ICF.
- Allocation of screening number.
- Documentation of demography (age, gender, race/ethnic origin).
- Physical examination (including vital signs: BT, BP, HR and RR) as per normal procedure.
- Documentation of relevant medical and surgical history.
- Review of Inclusion / Exclusion criteria to confirm subject pre-operative eligibility (i.e., oral Coumadin (warfarin) or Factor Xa inhibitors within 3 days prior to surgery and antiplatelet/P2Y12 medication within 5 days prior to surgery are exclusion criteria). If a subject is not eligible, the reason must be documented on the worksheet/screening log.
- CBC with Hgb test within 7 days prior to surgery.

11.2. Baseline Assessments (Within 24 Hours Prior to Procedure)

The following activities will be performed within 24 hours prior to the procedure. The timing of these activities may occur based on routine hospital practice and may overlap with some of the screening activities listed in Section 11.1.2.

- Review of inclusion / exclusion criteria to confirm subject pre-operative eligibility (i.e., subjects on heparin 12 hours prior to surgery is an exclusion criteria). If a subject is no longer eligible, the reason for the screen failure will be documented on the source documentation and screening log.
- Documentation of all concomitant medications beginning 24 hours prior to surgery.
- Documentation of any changes in medical history since the screening visit.
- Serum or urine pregnancy test (if applicable).
- Ensure subjects platelet count is $\geq 100,000$ per microliter and INR is < 1.5 prior

to 24 hours of surgery.

11.3. Preparation of SURGICEL Powder for Surgery

SURGICEL Powder device with “open tip” applicator is prefilled with 3 grams of powder. The SURGICEL Powder “open tip” and the endoscopic tip are supplied sterile and ready to use out of the package. Only undamaged packages should be used. Once the foil pouch is opened, re-sterilization is not possible. The following procedure for opening and applying the product should be followed to ensure that the sterility of SURGICEL Powder is maintained.

Non-sterile nurse / Study personnel

Open outer foil pouch and transfer SURGICEL Powder delivery device and inner card to sterile field. If an endoscopic procedure, repeat the above for both the SURGICEL Powder and the endoscopic accessory.

Sterile nurse / field

Hold the body of the applicator, remove SURGICEL Powder delivery device from inner card and twist to open.

SURGICEL Powder delivery device is now ready for use. If an endoscopic procedure, repeat the above and replace the “open tip” attachment with the endoscopic accessory as per the IFU/IB.

The opened product must remain in the sterile field to be available for use throughout the procedure but should be kept dry and should be discarded appropriately at the end of the procedure.

11.3.1. Dose, Route and Duration of Administration

For each subject, SURGICEL Powder and SURGICEL Original will be available and ready for administration prior to randomization.

Additional information may also be found in the Instructions for Use (IFU) and/or (IB).

11.3.2. Application of SURGICEL Powder

Apply an adequate amount of SURGICEL Powder to cover the entire TBS. Use of a non-adhering substrate to apply pressure may prevent adhesion of the formed clot to the surgical glove or other instrumentation.

11.3.3. Investigational Product Dispensation and Accountability

A dispensing log will be kept by the designated study personnel. This log will contain information on the date of administration, subject ID number, lot number, quantity of SURGICEL Powder or SURGICEL Original dispensed, details of any remaining product, subsequent destruction (if applicable). The study monitor will verify these logs during the course of the study. The study product will be stored according to the IFU and be kept in a secured area with access restricted. Study product is to be used for study subjects only.

11.3.4. Topical Hemostats

The use of any other topical hemostats will be permitted on non-target bleeding sites and must be used according to their respective labelling and the Investigator's usual practice. Details of all topical hemostats used for the subject throughout the procedure will be recorded on the Concomitant Medication eCRF.

11.3.5. Documentation of 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.

11.3.6. Randomization Procedure

Randomization will be stratified by investigational site and bleeding severity: mild or moderate bleeding. Sponsor will provide each site with computer-generated randomization envelopes, each bearing the subject randomization number, and containing the treatment allocation and stratification.

The identified TBS will be treated after stratification and randomization, based on the procedures described in this protocol. Treatment will be assigned randomly to each subject on a 1:1 basis to SURGICEL Powder or SURGICEL Original. If a potential subject fails intra-operative criteria (i.e., no TBS identified, or has an intra-operative exclusion), and is not enrolled in the study, the unused randomization envelope should be returned to the series, and used for the next subject.

This will be a single blinded study where the subject will be blinded to treatment. Subjects should remain blinded throughout the trial. Given the differences in appearance

of the two treatment groups, it will not be possible for the Investigator to be blinded to the treatment. However, to avoid any bias in the conduct of the surgical procedure, randomization should only take place after completion of the following steps:

1. SURGICEL Powder and SURGICEL Original will be available in the operating room for administration for each subject.
2. The Investigator must perform the surgical procedure according to his/her standard of care.
3. When the Investigator encounters the first appropriate TBS related to the primary operative procedure that requires an adjunct to achieve hemostasis because traditional methods have been determined to be ineffective or impractical, he/she should classify the severity of bleeding to be treated.
4. The subject will then be randomized immediately by opening the appropriate randomization envelope, based on stratification of bleeding severity.
5. The randomly assigned treatment article (SURGICEL Powder or SURGICEL Original) will be applied to the TBS immediately, per the IFU/IB of each product.

The subject will remain blinded to treatment throughout the study.

11.4. Surgical Procedure

The surgeon will use his/her standard surgical techniques for the surgical procedure.

SURGICEL Powder and SURGICEL Original will be available in the operating room ready for administration prior to randomization for each subject.

When the surgeon encounters the first appropriate TBS with mild or moderate bleeding in the parenchyma or soft tissue related to the primary operative procedure where conventional methods of control (i.e. suture, ligature, cautery) are ineffective or impractical, the subject may be considered for treatment with the randomized treatment.

11.4.1. Types of Surgical Procedures

Open, laparoscopic, or thoracoscopic surgical procedures may include the following surgical specialties:

- General
- Gynecological
- Cardiothoracic.

Examples of types of surgical procedures considered for this study may include, but are not limited to:

- Colectomy

- Low anterior resections
- Retroperitoneal tumor resection
- Liver resection
- Soft tissue bleeding after adhesiolysis
- Hernia repair
- Radical hysterectomy
- Lymphadenectomy
- Tumor removal surgery
- Diffuse bleeding on visceral or parietal pleura
- Soft tissue in cardiothoracic procedures.

11.4.2. Definition of Target Bleeding Site

The TBS will be defined as the first accessible bleeding site identified during dissection, related to the primary operative procedure requiring an adjunctive hemostat.

Once the TBS is identified and conventional techniques were considered impractical or ineffective, the surgeon will apply the randomized treatment at the TBS to cover the entire bleeding area. The bleeding severity will describe the intensity of the bleeding that is present at the time the surgeon determines that an adjunctive hemostatic product is required. At each investigational site enrollment will be stratified into two groups, according to TBS bleeding severity (mild or moderate bleeding).

As a frame of reference, only target bleeding sites with mild or moderate bleeding as defined by the following scale of bleeding intensity will be included:

Mild Bleeding: A TBS with a small area of capillary, arteriole, or venule oozing.

Moderate Bleeding:

1. A TBS with a larger area of capillary, arteriole, or venule oozing that presents a significant challenge because of the larger area involved, increasing the volume of blood loss.

or

2. A TBS with bleeding that is more pronounced than oozing, which could also

come from a small artery or vein, but is not massive, pulsatile, and flowing.

Severe Bleeding (excluded by this protocol):

Bleeding (arterial, venous, or mixed) that is rapidly flowing, pulsatile, or spurting, which in the surgeon's judgment requires rapid control to prevent hemodynamic consequences (e.g. hypovolemia, tachycardia, or hypotension) and could involve major volume loss which if not treated rapidly, could be life threatening. SURGICEL Powder and SURGICEL Original should not be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial or venous bleeding or major defects in arteries and veins.

11.4.3. Activities and Information Collected During Surgical Procedure

The following activities will be performed and the following information will be collected during the surgical procedure:

- Review of inclusion and exclusion criteria to confirm intra-operative eligibility. If a subject is no longer eligible, the reason for the screen failure will be documented in the source documentation and the screening log.
- Concomitant medications, as outlined in Section 11.3.5
- Hospital admission date (for overall Length of Stay)
- Entry and exit time.
- Primary surgical procedure information: open, laparoscopic, thoracoscopic. surgical specialty (general, cardiothoracic, gynecological and the type of procedure).
- Procedure time (first incision to final wound closure).
- Randomization, as outlined in Section 11.3.6.
- Assessment and determination of hemostasis at TBS
- Estimated Blood Loss (EBL)
- Transfusion information (if applicable). Amount and blood product(s) used and the type of product (e.g., red blood cells, fresh frozen plasma, platelet concentrate, etc.).
- Hemostatic methods used at the TBS prior to randomization (none, [other

methods are impractical], suture, ligation, cautery, other.

- TBS information: Parenchyma or soft tissue type and location
- Size of TBS (length, width)
- Heparin use and time of reversal (if applicable)
- Total number of units used (SURGICEL Powder or SURGICEL Original)
- Adverse events, including any complications possibly related or related to bleeding and/or thromboembolic events.
- Drain information (if applicable)
- Surgeon Ease of Use Questionnaire– one questionnaire needs to be completed per Investigator for their first 2 cases using SURGICEL Powder (completed as soon as possible, but within approximately 72 hours).

11.4.4. Treatment Application

Upon completion of application of the randomized treatment to the TBS, the stopwatch will be immediately started, (T0) and the time on the wall clock will be recorded.

Hemostasis will be assessed at 3 minutes, 5 minutes and 10 minutes post randomized treatment application and at initiation of fascial closure for all subjects.

Refer to the IFU/IB of each product for detailed instructions on the application of SURGICEL Powder and SURGICEL Original.

11.4.5. Subjects Randomized to SURGICEL Powder

After identification of the appropriate TBS, SURGICEL Powder should be applied according to the IFU.

Key Notes from SURGICEL Powder Labelling:

- SURGICEL Powder should be applied dry so should **not** be moistened with water or saline prior to application. Apply an adequate amount of SURGICEL Powder by compressing the bellows, to cover the entire TBS. Depending on the bleeding intensity and anatomical location, more than one layer may be needed to achieve complete hemostasis. After SURGICEL Powder application to the TBS, the surgeon may apply pressure over the treatment site, as needed. Use of non-adhering substrate to apply pressure may prevent adhesion of the formed clot to the surgical glove or surgical instrumentation.
- SURGICEL Powder is absorbable and may be left in situ, it is advisable to remove excess powder with irrigation and aspiration once hemostasis is achieved, without disturbing the clot.
- In the event of continued bleeding or re-bleeding at the TBS at any time prior to closure, the surgeon may add additional SURGICEL Powder, if clinically appropriate, or revert to their institutional standard of care.
- If the surgeon feels re-bleeding is due to insufficient coverage of the bleeding area, additional SURGICEL Powder may be applied.

11.4.6. Subjects Randomized to SURGICEL Original

After identification of the appropriate TBS, SURGICEL Original should be applied according to its labelled instructions.

11.4.7. Hemostasis Assessments

All hemostasis assessments at the TBS will be assessed the same regardless of randomization.

Table 2: Hemostasis Assessment (Time Table)

T₀	Start time. When randomized treatment application is complete (entire TBS covered)
T₃	TBS Bleeding assessment 3 minutes following T ₀
T₅	TBS Bleeding assessment 5 minutes following T ₀
T₁₀	TBS Bleeding assessment 10 minutes following T ₀
T_F	TBS bleeding assessment post the 10-minute assessment, immediately prior to the initiation of final fascial closure

11.4.8. Time to Hemostasis Assessment:

- The Investigator is required to call out once he/she has completed application of the product (defined as adequate coverage including additional layer, if needed) - at the same time, the stopwatch must be started and the wall clock recorded by study personnel (T_0).
- The TBS will be assessed at the time points 3 minutes (T_3), 5 minutes (T_5), and 10 minutes (T_{10}) following application for assessment of hemostasis.
- The Investigator must evaluate for hemostasis at the TBS immediately prior to the initiation of final fascial closure (last time TBS is visible to confirm hemostasis, T_F).
- Hemostasis will be defined as no detectable bleeding from the TBS.
- In the event of continued bleeding or re-bleeding at the TBS at any time prior to closure, the surgeon may add additional randomized treatment, if clinically appropriate, or revert to their institutional standard of care. Information on the treatment methods of re-bleeding/continuous bleeding at the TBS must be recorded.

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

- During the 10-minute assessment period and following the initial application of the randomized treatment, the surgeon may reapply randomized treatment. The subject will be considered a failure for preceding binary primary and secondary effectiveness endpoints [e.g. if subjects achieve hemostasis 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 the randomized treatment does not have an impact on the success/failure evaluation of subsequent binary effectiveness endpoints (e.g. if hemostasis is achieved by reapplication of randomized treatment, the subsequent binary endpoints will not be impacted. If an additional randomized product is applied to the TBS and the TBS is hemostatic at the 10-minute assessment period and maintained up until 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 hemostatic measures (other than additional application of randomized treatment), 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 hemostatic 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.

11.5. Post-Surgery until Hospital Discharge

Prior to discharge, the following data will be recorded:

- Changes in concomitant medications.
- Was drain used, if yes record days, quantity and describe content (type of the discharge, e.g. serosal fluid, blood, etc.).
- Physical examination (vital signs: BT, BP, HR and RR) for 3 consecutive days or until hospital discharge, whichever comes first.
- CBC with Hgb test prior to discharge.
- Adverse events, including reoperation, any complications possibly related to bleeding and/or thromboembolic events.
- Date of hospital discharge (for overall Length of Stay).

11.6. 30-day Follow-Up Phone call or Office Visit (+ 14 days)

The following information will be recorded at the clinical follow-up phone call or office visit approximately 30 days following the study surgery:

- Changes in concomitant medications, including use of any blood products following hospital discharge.
- Adverse events, including any reoperations and/or complications possibly related or related to bleeding and/or thromboembolic events.

11.7. Six-Month Follow-Up Phone Call or Office Visit (+/- 30 days)

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

- All SAEs that were ongoing at the 30-day post-surgery visit will be followed until completion of the 6-month follow-up phone call or office visit, or until a stable resolution, whichever comes first.

12. MONITORING PLAN

This study is performed according to the Good Clinical Practice for Medical Product Trials and related laws and regulations.

The Sponsor bears the monitoring responsibility for the clinical trial and will select the qualified monitor to execute the monitoring responsibility.

The monitor should comply with the related laws and regulations and the standard operating procedure established by the Sponsor with regard to the monitoring to monitor each phase of this study.

The monitor should contact and visit the investigators at a regular basis and make the field visit/monitoring for the study. The monitor should make a visit when the first subject is enrolled, and make a necessary visit at a regular basis (about every 4 or 6 weeks) during the study period.

The monitoring includes the visit to clinical trial institution, verification of CRF data, communication with investigators and clinical trial institution, ensuring that this study will be performed strictly in compliance with the trial protocol and the requirements of regulations of Good Clinical Practice, etc.

The on-site inspection of CRF includes verifying the source document and checking whether original data is true, accurate, complete and clear, the original document of each subject is complete.

This study may be subject to the audit by the Sponsor or regulatory authority. If such audit is performed, the Investigator must agree the auditor to look up the records of subjects. The Investigator agrees the Sponsor or its appointed representative and regulatory authority to monitor all project-related study documents on site by signing on the signature page of this trial protocol.

13. STATISTICAL CONSIDERATIONS

13.1. 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 after TBS identification will be included in the ITT.
- 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.
- Safety analysis set consists of all subjects who received study product.

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

All secondary effectiveness endpoints will be analyzed using the ITT set, while safety endpoints will be analyzed 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 are deviations that have an impact on the primary effectiveness endpoint. These will be determined prior to database lock.

13.2. Statistical Design, Method and Analysis Procedure

This is a single blind, randomized, prospective study comparing SURGICEL Powder with SURGICEL Original (control) 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 patients.

Subjects will be randomly assigned to either SURGICEL Powder (Test) or SURGICEL Original (Control) in a 1:1 allocation ratio. Randomization will be stratified by investigational site and TBS bleeding severity (mild or moderate bleeding).

Two analyses will be performed. The first analysis will occur after all subjects complete phone call or office visit [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 phone call or office visit [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 or related to the randomized study treatment.

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.

This is a non-inferiority trial with a 10% margin and the statistical analysis comparing treatment groups for primary effectiveness endpoint performed at one-sided significance level of 0.025 and 80% power. The true success rates are assumed to be 85% in the SURGICEL Powder (Test) group and 80% in the SURGICEL Original (Control) group.^{14, 15, 16, 17}. For the justification of the assumed success rates in the two treatment groups, see Section 7.

Study Hypothesis

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

- $H_0: P_T - P_C \leq -0.1$ tested against the alternative hypothesis
 $H_1: P_T - P_C > -0.1$ P_C proportion of successes in Control group, and
 P_T is the proportion of successes in Test group.

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 SURGICEL 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.

The primary endpoint will be analyzed using the Intent-to-Treat (ITT) and Per-Protocol (PP) sets. The PP analysis will be considered the primary analysis, while the ITT analysis will be considered supportive. The analysis sets for this study are defined in Section 13.1.

The following **secondary efficacy endpoints** will be summarized descriptively by treatment group and overall, for the ITT analysis set:

- 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.

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, the following **safety endpoints** will be summarized descriptively by treatment group and overall, for the Safety analysis set:

- Incidence of thromboembolic events that were assessed as possibly 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 or related to the TBS 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 or related to the study treatment (from enrollment through the 6-month follow-up phone call or office visit)

The incidence of adverse events (AEs) will be assessed at the preferred term level using the Medical Dictionary for Regulatory Activities (MedDRA) for event categorization. Incidence of AEs will also be assessed by onset time (intraoperative or postoperative), relationship to study surgical procedure, relationship to the study product, severity, and seriousness.

All continuous variables will be summarized by number of subjects, mean, standard deviation, median, minimum and maximum. All categorical data will be summarized by frequencies and associated percentages. No inferential statistics will be generated for

secondary efficacy and safety endpoints.

13.3. Calculation of Sample Size

13.3.1. Total Sample Size

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 subjects (117 per treatment arm) will be randomized into the trial in a 1:1 allocation ratio SURGICEL Powder to SURGICEL Original.

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.

13.3.2. Minimum and Maximum Number of Subjects in Each Clinical Trial Institution and Reasons for Determination

A total of 234 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).

13.4. Significance Level and Power of Clinical Trial

The power of the statistical test at which the sample size for the primary endpoint was calculated is 80%, and the one-sided significance level of the test was set to 0.025.

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. 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.

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.

13.5. Expected Dropout Rate

The expected dropout rate in this study is 10%.

13.6. Criterion of Acceptability/Unacceptability of Clinical Trial Result

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 SURGICEL 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.

13.7. Criteria and Reason for Terminating the Trial Based on the Statistical Results

13.8. Early termination of this trial is not applicable since no formal interim analyses are planned. Statistical Method of All Data, together with the Handling Method of Missing, Unused and Error Data (including Termination and Withdrawal Halfway) and Unreasonable 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 will not be imputed.

13.9. Reporting Procedure of Deviation from Original Statistical Plan

Any changes from the original planned statistical analyses will be specified in the protocol revisions, if applicable, and/or in a final or amended statistical analysis plan. The impact of these changes on any conclusions of the study will be detailed in the final Clinical Study Report.

13.10. Selection Criteria and Reason of Subjects Included in the Analysis

All subjects that meet the inclusion/exclusion criteria are considered to meet the requirements for recruitment. Definitions of analysis sets are included in Section 10.1.

14. DATA MANAGEMENT

The individual subject data collected during the period of this trial will be recorded in the corresponding study database. The captured data will be reviewed by the data

management team and other applicable Sponsor study team members. Any unexpected or missing data points will generate a query for the site to assess and resolve. Sponsor provided monitors will be available for questions and follow-up with the sites, as needed.

When all subjects complete all follow-up evaluations and the corresponding data is entered, this study will be closed and the data analysis will be performed following database lock.

15. FEASIBILITY ANALYSIS

15.1. Likelihood Analysis of Success

Adjunctive topical hemostatic agents have been utilized for over 100 years. The equivalent comparator to SURGICEL Powder, SURGICEL Original, has been available for more than 50 years, introduced in 1960 with a long history of safe and efficacious use.

SURGICEL Original and its family of products has predominately been used to assist in achieving and accelerating hemostasis, during which several types of bleeding have been observed intra-operatively. These types of products are optimal when bleeding is confined, because the product can be placed on the source of bleeding with manual compression to facilitate hemostasis. When bleeding is not confined, continuous oozing from large friable and raw surfaces can cause delays and surgeon frustration during surgery. These situations require ready to use hemostatic products with minimal or no preparation time and in addition must be able to achieve quick coverage on the bleeding surface and the ability to achieve hemostasis.

SURGICEL Powder, an optimized powdered form of ORC, is a topical absorbable hemostat being evaluated in this study to further measure its safety and hemostatic effectiveness in controlling mild to moderate parenchymal or soft tissue intra-operative bleeding. Although there is sufficient information supporting the safety and performance of SURGICEL Powder supported by data from acute and survival preclinical studies (see Section 8), this registration study will be implemented to further enhance our understanding of safety and performance of SURGICEL Powder in a real world clinical setting.

15.2. Likelihood Analysis of Failure

In recent years, adjunctive topical hemostatic agents are gaining momentum in China. Because of this growing popularity as well as the state of the art optimized powder form of ORC, failure to meet total enrolment (234 patients) as stipulated by the protocol, is

unlikely. Also, because of the long history of safe and efficacious use of the SURGICEL family of products, it is unlikely that the study will be discontinued because of safety concerns.

16. PRODUCT MANAGEMENT

All products must be stored in conditions according to product labeling and IFU/IB. It is the responsibility of the Principal Investigator to ensure that products are stored correctly at the site.

The Principal Investigator or responsible person designated by the Principal Investigator must account for all study products throughout and, at the end of, the clinical study. During the course of the study, the study products must be stored in a locked or secure access location. An inventory record must be maintained of all products received, used or returned during the clinical trial. Details of the product code and lot numbers must be documented in the CRF as well as the subject's hospital notes. The Principal Investigator must allow the Monitor access to the secure facility where the study products are stored during the clinical trial in order to check inventory. At the end of the clinical trial all unused study products must be returned to Johnson & Johnson Medical (Shanghai) Ltd. with the appropriate study product return form.

17. QUALITY CONTROL OF CLINICAL TRIAL

During the clinical study, the Sponsor and Investigator should execute their respective responsibilities according to the Good Clinical Practice for Medical Product Trials and applicable related Chinese and international regulations. They should also strictly follow the clinical trial protocol to ensure the quality of clinical trial.

The Sponsor will ensure proper training on the clinical trial protocol and the use and maintenance of investigational medical product for all investigators participating in the trial, so as to ensure the consistency in the implementation of clinical trial protocol, the use of investigational medical product.

During the implementation of study, the Sponsor is responsible for monitoring each phase of the clinical trial. The clinical monitor employed by the Sponsor or appointed representative should comply with the related standard operating procedure (SOP) and clinical trial protocol that are established by the Sponsor to monitor the clinical trial, so as to ensure the complete, accurate, true and reliable data.

To ensure the quality of study, the Sponsor may authorize the eligible QA auditor to audit the clinical trial, as needed. The Investigator should allow the auditors to review the

original data and documents related to this study after receiving the notification.

When the food and drug regulatory authority, competent department of health and family planning or other regulatory agencies send the inspection personnel to carry out the inspection, the clinical trial institution and Investigator should cooperate and immediately notify the Sponsor.

18. CLINICAL TRIAL-INVOLVED ETHICAL ISSUES AND INFORMED CONSENT

18.1. Ethical Concerns

Participating Investigators will ensure that this protocol, the ICF, and if applicable, any protocol amendments or other written information provided to the subjects that assist in the decision to participate are reviewed by an Institutional Review Board (IRB) or Ethics Committee (EC) that complies with governmental requirements. The approving IRB/EC will be responsible for the initial and continuing review and approval of this clinical investigation. Participating investigators will be required to promptly report to the IRB/EC as required by the IRB/EC's policies. Additionally, investigators will be required to refrain from making any changes in the clinical investigation plan without Sponsor and IRB/EC approval of an amended protocol, except where necessary to eliminate apparent immediate hazards to study subjects or others.

Before the subjects participate in the clinical trial, the Investigator must fully explain this study and answer all questions raised by subjects. Each subject (or legally authorized representative) must voluntarily sign and date the informed consent form (and other documents as per local regulations) that is approved by the Ethics Committee prior to implementing any study-related tests or procedures which are not SOC. The process of obtaining the informed consent needs to be clearly documented in the original record of the subject. The subject may request to withdraw the informed consent at any time during the study. This withdrawal will not affect the subsequent therapy of available / provided to the subject.

The production of investigational product should meet the relevant requirements of applicable quality management system for medical products. The processing and storage of investigational product should meet the requirements of specifications and related standard operating procedure. The investigational product should be used according to the approved protocol and related operation instructions and IFU/ IB.

The collection, use and disclosure of all personal data (including the subject health and medical information) should comply with the applicable laws and regulations with regard

to the personal data protection and security. When collecting and processing such personal data, appropriate measures are to be taken to maintain the confidentiality of subject health and medical information and to prevent access by unauthorized persons.

18.2. Approval of Trial Protocol

The trial protocol should be internally approved and filed according to the company's SOP prior to submitting to the external agency (including but not limited to the government regulatory agencies, Ethics Committee).

The clinical trial protocol should not be implemented until the written approval is obtained from the Ethics Committee according to the relevant requirements of laws and regulations.

18.3. Process of Informed Consent and Text of Informed Consent Form

18.3.1. Process of Informed Consent

The informed consent of all potential subjects must be obtained prior to performing any study tests/procedures that are not SOC. Once the Investigator determines that the subjects are suitable for participating in this study, the Investigator must explain the background of the study presented and the benefits and risks of surgery and study to the subjects and answer the questions raised by subjects. Only the subject who signs the informed consent form that is approved by the EC prior to participating in the study is eligible to participate in this study.

Each subject (or legally authorized representative) must sign and date the informed consent form that is approved by the EC (and other documents as per local regulations) prior to implementing any study-related items or operations not belonging to the standard treatment and after the nature of this study is fully clarified.

The process of obtaining the written informed consent needs to prove that the subjects volunteer to participate in this study. All aspects of this study must be clarified to the subjects prior to signing the informed consent form. The process of obtaining the informed consent must be clearly documented by the Investigator and/or designated person in the original clinical trial documents of subjects. The Investigator has responsibilities to ensure the process of obtaining the informed consent is implemented according to the Good Clinical Practice for Medical Product Trials and related regulations, such as ISO 14155, the Declaration of Helsinki.

18.3.2. Text of Informed Consent Form

The ICF is available as a separate attachment.

19. REGULATIONS OF ADVERSE EVENT AND PRODUCT COMPLAINT REPORTING

19.1. Adverse event

Adverse Events associated with the device, or the procedure, and incidents such as those specified in local laws and regulations will be captured and reported during this study. Monitoring of study sites by Sponsor personnel will ensure that adverse events and product complaints are documented.

19.2. Definitions

19.2.1. Pre-existing Condition

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.

To avoid confusing pre-existing conditions with AEs during data analysis, the study sites must make all attempts to provide start dates for all baseline medical conditions. Any pre-existing condition that has worsened in intensity, frequency, or the character of the condition should be recorded on the AE eCRF as an exacerbation of the pre-existing condition and the start date will be recorded as the time when the exacerbation occurred.

19.2.2. Adverse Event

For this study, an AE is 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.

19.2.3. Adverse Device Effect

An Adverse Device Effect (ADE) is an adverse event related to the use of a study medical device. This includes any adverse event resulting from insufficient or inadequate Instructions for Use, deployment, implantation, or operation, or any malfunction of the study medical device. An ADE may also include any event resulting from use error or from intentional misuse of the study medical device.

19.2.4. Unexpected Adverse Device Effect

An unexpected ADE is an adverse device effect, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure or product labelling).

19.3. Serious Adverse Event

It is the investigator's responsibility to determine the "seriousness" of an AE using the protocol defined terms below. An SAE is any AE that results in any of the following:

- Death or a life-threatening event.
- Inpatient hospitalization or prolongation of hospitalization.
- Persistent or significant disability/incapacity.
- Congenital anomaly/ birth defect//led to fetal distress, fetal death

Notes:

1. "Death" should not be reported as an AE. The cause of death should be reported as an AE. The only exception is "Sudden Death," when the cause is unknown.
2. Planned hospitalization for a pre-existing condition is not considered an SAE.
3. A procedure required by the protocol is not considered an SAE, unless the subject experiences a serious deterioration in health or hospitalization is prolonged.

Enrollment through 30-Day Follow-Up: All SAEs, whether attributable to the device/procedure, are to be recorded in the eCRF and reported to the Sponsor.

6-Month Follow-Up: SAEs requiring surgical intervention and assessed as possibly related or related to the study treatment are to be recorded in the eCRF and reported to the Sponsor.

Follow-up on all SAEs possibly related or related to the study treatment, which were ongoing at the 30-day post-surgery follow-up will be assessed.

19.3.1. Serious Adverse Device Effect (SADE)

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

19.3.2. Unexpected Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: Expected serious adverse device effect is an effect which by its nature, incidence, severity or outcome has been identified in the IFU/IB.

19.4. Severity of Adverse Events

It is the Investigator's responsibility to assess the severity of an AE. A change in severity may constitute a new reportable AE. The following guideline should be used to determine the severity of each AE:

- **MILD:** Awareness of experience, but easily tolerated. No medical intervention required.
- **MODERATE:** Enough discomfort to interfere with usual activities. Medical intervention required.
- **SEVERE:** Inability to carry out usual activities. Medical intervention (including hospitalization or prolongation of hospitalization) required.

19.5. Relationship/Attribution of Adverse Events

It is the Investigator's responsibility to assess the relationship of an AE to the study procedure and study device(s).

The following guideline should be used in determining the relationship of an adverse event to the study device, study procedure, or other causality:

- Not related
- Unlikely
- Possible
- Probable
- Causal relationship.

19.6. Reporting Adverse Events

Enrollment through 30-Day Follow-Up: All adverse events (both serious and non-serious), whether attributable to the device/procedure or not, will be reported from time of enrollment, during the surgical procedure, and until completion of the 30-day follow-up. The Investigator will evaluate the severity of the event, and its relatedness to the study device or procedure and the information will be entered in the AE eCRFs.

6-Month Follow-Up:

Follow-up on all SAEs possibly related or related to study treatment, which were ongoing at the 30-day post-surgery follow-up will be assessed.

SAEs requiring surgical intervention and assessed as possibly related or related to the study treatment will be reported at the 6-month follow-up. The Investigator will evaluate the severity of the event, and its relatedness to the study device or procedure and the information will be entered in the AE eCRFs.

Any necessary medical management of the event will be recorded in the subject's medical record/source document.

The Investigator will record all AEs (both serious and non-serious) in the source documents. CTC (Common Terminology Criteria) should be used when recording AEs. In addition, the following information should be recorded:

- Onset date
- Resolution date or date of death
- Severity of the event
- Action taken
- Event status (ongoing at study end or resolved)
- Relationship of AE to the study treatment
- Relationship of AE to the study procedure
- Indication of seriousness.

19.6.1. Reporting Serious Adverse Events to the Sponsor

Enrollment through 30-Day Follow-Up:

The study site must report all SAEs, whether they are related to the device or procedure, to the Sponsor within 24 hours of becoming aware of the SAE.

6-Month Follow-Up:

The study site must report SAEs requiring surgical intervention and assessed as possibly related or related to the device or procedure to the Sponsor within 24 hours of becoming aware of the SAE.

The study site will report SAEs by entering the event into the EDC system via the Adverse Event eCRF, which will trigger an automated email to the Sponsor. Additional information, including the Investigator's assessment, may be added to the eCRF later; however, the study site must complete the AE eCRF within 24 hours of becoming aware of the SAE. If the Sponsor requires supporting documentation or other information, the Sponsor will contact the study site.

In the event of death, the Investigator must report all available information to the Sponsor.

The report of an SAE by a site does not constitute an admission that study personnel or the user facility (hospital/clinic) caused or contributed to the event. The study site is responsible for submitting AEs to the reviewing IRB/EC, per their IRB/EC procedures.

19.6.2. Reporting Non-Serious Adverse Events to the Sponsor

Enrollment through 30-Day Follow-Up:

All non-serious AEs, whether attributable to the device/procedure or not, will be reported from time of enrollment, during the surgical procedure, and until completion of the 30-day follow-up. For all non-serious AEs, the study site is expected to complete the Adverse Event eCRF within 2 weeks of becoming aware of the event. Supporting documentation may be requested, as needed.

19.6.3. Reporting Unanticipated Adverse Device Effects to the Sponsor

The study site must report all UADEs to the Sponsor within 24 hours of becoming aware.

Information not available at the time of the initial report (e.g., an end date for the UADE) must be updated within [REDACTED]. In the event of a fatal or life-threatening event, any required follow-up information must be submitted to the Sponsor immediately, but no later than 10 calendar days of the initial report.

If the Sponsor determines an UADE presents an unreasonable risk to subjects, the Sponsor shall terminate all or a portion of investigations as soon as possible so as not to jeopardize the health of any subject.

Termination shall occur no later than 5 working days after the Sponsor makes this determination and no later than 15 working days after the Sponsor first receives notice of effect. Resumption of terminated studies can occur only with IRB/EC and Health Authority approval.

Other: The Investigator may also need to consider whether an event is attributable to the investigational product, based on insufficiencies or inadequacies in the instructions or as a result of user error. The Investigator must contact the Sponsor should this occur.

19.7. Product Complaint Definition

A product complaint is defined as any written, electronic or oral communication that alleges deficiencies related to the identity, labelling, quality, durability, reliability, safety,

effectiveness, or performance of a device after it is released for distribution. A product complaint may or may not be associated with an AE/SAE.

Product complaints may include, but are not limited to:

- Product contamination;
- Defective components;
- Poor packaging or product mix-up;
- Questionable stability;
- Device malfunction (the failure of a device to perform as intended for this study);
- Labelling concerns;
- User errors.

19.8. Reporting Product Complaints

Product complaints must be reported to the Sponsor in a timely manner. For all UADEs, the Sponsor must be notified within 24 hours of the site becoming aware. If an Ethicon representative is made aware of a product complaint related to the study device, the event should be reported within 24 hours of their awareness.

Product Complaint should be emailed to:

Global CHU: Productcomplaint1@its.jnj.com

Local CHU reporting: ChinaCustomerQuality-CS@its.jnj.com

20. DEVIATION FROM CLINICAL TRIAL PROTOCOL AND REGULATIONS FOR CLINICAL TRIAL PROTOCOL AMENDMENT

The study protocol deviations are defined as the circumstances that fail to comply with the requirements of clinical trial protocol intentionally or unintentionally.

All protocol deviations should be reported as protocol deviations to the Sponsor via the study EDC database. The reporting should include the date and reason for protocol deviations. The Investigator should also report the protocol deviations to the EC and all related department according to the site requirements and in combination with the requirements and procedures of the EC.

If a protocol amendment occurs, the Sponsor or designated person should submit a summary of changes of the study protocol to the Investigator, regulatory authority, and

the Ethics Committee, etc. according to the relevant laws and regulations. All major amendments must be approved by the Ethics Committee and regulatory authority (if needed) prior to implementing any changes to study procedures.

If an amendment likely has major impact on the following items, this amendment belongs to the major amendment:

- Safety or physical or mental health of subjects;
- Scientific value of trial;
- Implementation or management of trial;
- Quality or safety of investigational medical product specified in the trial.

21. DIRECT ACCESS TO SOURCE DATA AND DOCUMENT

The source data is defined as all information in the original record and its approved copy with regard to the clinical findings, observations and other activities in the clinical trial, which can be used for reproduction and evaluation of clinical trial. The source documents are documents on which the source data is recorded, including printed, paper or electronic documents.

The subject's medical record and other study related documents (source documents) must be maintained and retained by the Investigator. The Investigator should allow the monitors and auditors/inspectors to review all relevant subject records, including but not limited to the following information:

- Medical/physical condition of the study subject that meets the inclusion criteria prior to participating this study;
- Process of informed consent;
- Operational description of use and implantation of the study product;
- All inspection results and follow-up;
- Examined printed output file or report (for example, X-ray film) that is dated and signed;
- Description of AE and follow-up of AE (description of event, severity, date of occurrence, duration, correlation with the study product, study procedure, outcome, and treatment of the AE, concomitant medications when the AE occurs);
- Description of product complaint;

- Study subject's status at the end of the study or withdrawn from the study.

Appropriate source documents must be available for reviewing during the monitoring visit. The Sponsor expects that the study coordinator and/or Investigator will also be available for questions during monitoring visits.

22. FINANCES AND INSURANCE

See the relevant study contract and insurance document.

23. CONFIDENTIALITY

The personal data of the subject participating in the trial is confidential; however, the Ethics Committee, CFDA, competent department of health and family planning, or the Sponsor and its authorized representative may review the personal data of the subject participating in the trial for the purpose of their work according to the local established procedure.

The personal data of the subject should be kept confidential during the entire period of clinical trial, and it should be ensured that the source data can be verified through the supporting information. A unique subject ID number (site number and subject number) will be used to identify all data for every enrolled subject. So long as the data is kept strictly confidential and that the privacy of the subject is ensured to be protected, the data related to this study may be available to third parties (for example, under the audit of regulatory authority).

24. AGREEMENT ON THE PUBLICATION OF TRIAL RESULTS

Following completion of this study, an article might be prepared and published in a scientific journal. No major results or experience from any individual site in this study are allowed to be published before the multicenter trial results are prepared and published. An exception to this rule will need prior approval from the Sponsor. A second publication may be generated by corresponding principal authors. The final analysis and review from all trial data are required to be reviewed and approved by the Sponsor.

25. RESPONSIBILITIES THAT EACH PARTY SHOULD BEAR

25.1. Responsibilities of the Sponsor

- 1) The Sponsor is responsible for the initiation, application, organization and monitoring of clinical trial.
- 2) The Sponsor is responsible for the organization to establish and modify the investigator brochure, clinical trial protocol, informed consent form, Case Report Form, relevant standard operating procedure and other relevant documents, carry out the training required for the clinical trial, and provide these documents to the investigators before the study starts.
- 3) The Sponsor should select the qualified trial institution and investigators.
- 4) The Sponsor should sign a written agreement with the clinical trial institution and the Investigator with regard to the clinical trial.
- 5) The Sponsor should provide qualified study product according to the regulatory requirements. The Sponsor should be responsible for the safety of investigational medical product in the clinical trial. The AE, SAE, and the product complaint that may cause an SAE should be collected and reported in accordance with the provisions.
- 6) The Sponsor should inform the regulatory authority at every level when the Sponsor decides to suspend or terminate the clinical trial or at the end of the study.
- 7) The Sponsor should ensure the Investigator conducts the study strictly in compliance with the clinical trial protocol, corrects the protocol deviations in a timely way, and reserves the rights to report, to the regulatory authority, any of issues related to this.
- 8) The Sponsor should bear the treatment cost and relevant economic compensation for the clinical trial-related injury or death of subjects, with the exception of damages due to the fault of medical institution and medical staff in the diagnosis and treatment.
- 9) The Sponsor should select qualified monitors for monitoring and organizing any inspections, as appropriate.

25.2. Responsibilities of Clinical Trial Institution and Investigator

- 1) The clinical trial institution should evaluate the relevant resources according to the features of investigational medical product prior to the clinical trial, so as to decide whether to participate in this clinical trial.
- 2) The clinical trial institution should properly keep the records and documents of clinical trial according to the agreement with the Sponsor.
- 3) Make sure that the Investigators responsible for the clinical trial have the qualification in accordance with the requirements of related laws and regulations.
- 4) The administrative department for clinical trial of medical product of clinical trial institution should cooperate with the Sponsor to apply to the Ethics Committee and submit the relevant documents prior to the clinical trial according to requirements.
- 5) The Investigator should ensure that the relevant workers participating in the trial have the enough resources and proper training, and keep the training related documents.
- 6) The Investigator should ensure to use the investigational medical product only for the subjects of this clinical trial, and may not charge any fee.
- 7) The Investigator should strictly follow the clinical trial protocol, with the exception of emergency circumstances when the subject faces the direct risk and needs immediate clinical measures, which can be reported later in a written form.
- 8) The Investigator is responsible for recruiting the subjects, communicating with the subject or its legal representative before signing the informed consent.
- 9) The Investigator should protect the rights, safety and health of the subjects.
- 10) In case of an AE occurring in the clinical trial, the Investigator should protect the safety of the subjects and timely report the event to the regulatory authority.
- 11) The Investigator should record all AEs occurring and product deficiencies found in the process of clinical trial, work with the Sponsor to analyze the causes of the events, generate the written analysis report, present the comments on the continuation, discontinuation or termination of the trial, and report to the Ethics Committee by the administrative department for clinical trial of medical product of clinical trial institution for review.
- 12) The Investigator should make sure that the clinical trial data is accurately, completely,

clearly and timely recorded in the Case Report Form.

- 13) The clinical trial institution and Investigator should make sure that the data, documents and records generated in the clinical trial are timely, true, accurate, clear, and attributable.
- 14) The clinical trial institution and Investigator should accept and cooperate with the monitoring and audit of the Sponsor, the supervision of the Ethics Committee, and the inspection of the Food and Drug Administration, competent department of health and family planning, etc., and provide all required records related to the trial.
- 15) If the clinical trial needs to be suspended or terminated, the subjects should be informed accordingly. It should be ensured that the subjects receive the proper care and follow-up. The clinical trial institution and Investigator should also report this in accordance with the regulations and provide a detailed written explanation. The relevant report should be submitted to the local Food and Drug Administration at the provincial, autonomous regional and municipal level, if necessary.
- 16) The clinical trial institution and Investigator reserve the rights to report to the regulatory authority at every level when the Sponsor violates relevant laws and regulations.
- 17) The Investigator should complete all records and reports at the end of clinical trial. The Investigator should also ensure that the received investigational medical products are properly handled and recorded according to the requirements.

25.3. Responsibilities of other interested parties

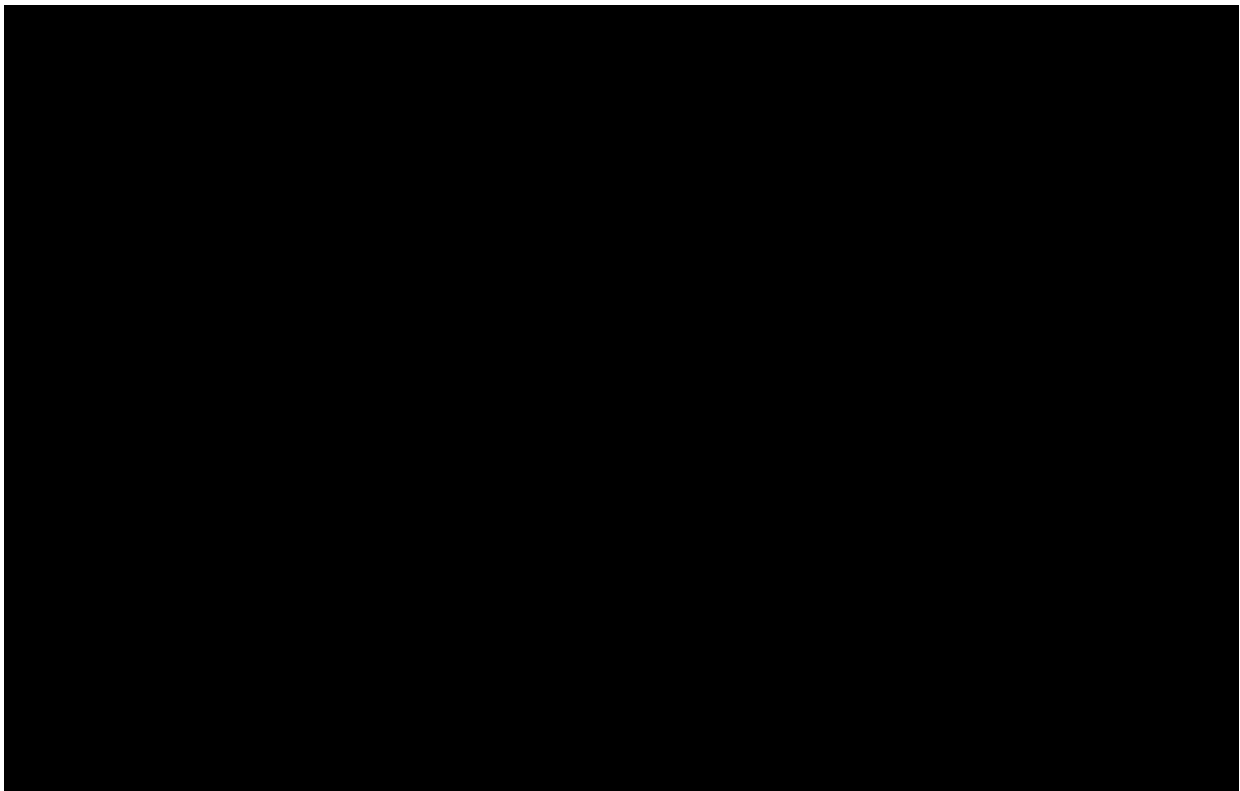
See the study related contract, which is available as a separate attachment.

STATEMENT OF INVESTIGATOR

I agree to:

1. Conduct this clinical trial in strict accordance with the requirements of the Declaration of Helsinki, China's current laws and regulations and trial protocol.
2. Record all required data correctly in the study EDC database and input, review, and approve the clinical trial report on schedule.
3. Use the investigational medical product only for this clinical trial, accurately and completely record the investigational medical product receipt and use condition during the clinical trial, and keep these records for review.
4. Allow the monitor and inspectors authorized and dispatched by the Sponsor and regulatory authority to monitor, inspect and audit this clinical trial.
5. Strictly implement the terms in the clinical trial contract/protocol signed by all parties.

I have read thoroughly the clinical trial protocol, including the above statements, and I agree to all the above contents.



26. APPENDICES

26.1. Appendix 1: United States Center for Disease Control (CDC) Guideline for Prevention of SSI Surgical Wound Classification

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.

26.2. Appendix 2: REFERENCES

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