Clinical Research Protocol

INVESTIGATIONAL DEVICE:	HemoStyp
STUDY NUMBER:	UHP001 Amendment No 1: 02 July, 2019
PROTOCOL TITLE:	Efficacy and Safety of HemoStyp as an Adjunct for Management of Secondary Hemostasis in the Operative Setting
STUDY PHASE	Pivotal
SPONSOR:	United Health Products, Inc. 1225 Vista Del Monte DR Mesquite, NV 89027
ORIGINAL PROTOCOL DATE:	10 September 2018
VERSION NUMBER:	1.2
VERSION DATE:	02 July 2019

United Health Products
Clinical Research Protocol

Efficacy and Safety of HemoStyp as an Adjunct for Management of Secondary Hemostasis in the Operative Setting

Protocol Number:	UHP001
Version Date:	08 July 2019
Investigational Device:	HemoStyp
IDE Number:	
Study Phase:	Pivotal Study
Sponsor	United Health Products, Inc. 1225 Vista Del Monte DR Mesquite, NV 89027 Contact: Gerard Abate, MD Phone: 540-220-6216 Email:gabate2521@gmail.com
Funding Organization:	United Health Products, Inc.
Primary Investigator (PI):	Name: Telephone: Fax: E-mail:

Approval:

_____ _____

PI or Sponsor Signature (Name and Title) *Date*

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing United Health Products with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: UHP001

Protocol Title: Efficacy and Safety of HemoStyp as an Adjunct for Management of Secondary Hemostasis in the Operative Setting

Protocol Date: 06 December 2018

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Investigator Signature *Date*

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Print Name and Title

Site Name _____

Address _____

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Phone Number _____

1 PROTOCOL SYNOPSIS

Title:	Efficacy and Safety of HemoStyp as an Adjunct for Management of Secondary Hemostasis in the Operative Setting
Protocol Number:	UHP001
Investigational Device	HemoStyp
Sponsor:	United Health Products, Inc. 1225 Vista Del Monte DR Mesquite, NV 89027
Funding Organization:	United Health Products, Inc.
Number of Sites:	10-15 sites
Number of Subjects:	236 subjects
Phase:	Pivotal Study
Study Design	This study is a prospective, non-inferiority, multi-center, randomized, open-label trial to compare HemoStyp with Surgicel® in the management of bleeding during surgery.
Objectives:	To assess efficacy and safety of HemoStyp as an adjunct for management of secondary hemostasis in the operative setting.
Subject Selection Criteria:	Inclusion Criteria: Subjects will be eligible to participate in this study if they meet all of the following criteria: 1. Elective procedure (non-laparoscopic thoracic, abdominal, or vascular surgery); 2. At time of surgery has mild to moderate soft tissue, vascular or parenchymal bleeding present at target bleeding site after primary standard conventional surgical hemostatic methods are proven to be ineffective or impractical; 3. Ages: Adult subjects ≥18 years of age; and 4. Subjects who are willing and able to sign consent. Exclusion Criteria: Subjects will not be eligible to participate in this study if they meet any of the following criteria: 1. Physical or psychological condition which would impair study participation; 2. Indications for emergency surgery; 3. Pre-operative laboratory findings of a hematologic disorder; 4. Subjects with history of moderate to severe allergies; 5. Subjects undergoing minimally invasive laparoscopic surgery; 6. Subjects who will require platelet or fresh frozen plasma transfusion during surgery; 7. Subjects who are pregnant or breast-feeding at the time of surgery; or 8. Subjects on P2Y12 platelet inhibitor (Plavix) less than 5 days prior to surgery, warfarin or Xa inhibitors not withheld per standard protocols for the management of anticoagulants pre-operatively. 9. Patients with a coagulation disorder, thrombocytopenia, liver disease and

anti-thrombin therapy.

Investigational Device/ Intended Use	HemoStyp is an absorbable hemostat composed of oxidized regenerated cellulose to be used as an adjunct to primary hemostasis in surgical procedures to assist in controlling capillary, venous and small arterial hemorrhage when other conventional methods are ineffective or impractical.
Control Group or Other Study Arms (if applicable)	Surgicel® Absorbable Hemostat (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.
Duration of Subject Participation and Study Duration:	Subjects will be in the study for up to 43 days Screening: Up to 10 days pre-operatively for elective surgery Treatment: Intra-operatively Follow-up: 30 days
Prohibited Concomitant Medications:	Anticoagulants, anti-platelets.
Efficacy Evaluations	The primary performance endpoints include: • Time to hemostasis from start of study treatment at target bleeding site until 10 minutes after treatment initiation. The non-inferiority of HemoStyp versus Surgicel will be evaluated. . Secondary efficacy endpoints include: • Percentage of subjects achieving hemostasis at the target bleeding site at 2 minutes, 5 minutes and 10 minutes following the start of study treatment; • Percentage of subjects with intraoperative hemostasis at the target bleeding site; • Percentage of subjects with intraoperative re-bleeding from the target bleeding site post hemostasis; and • Percentage of subjects with postoperative re-bleeding from the target bleeding site requiring surgical re-exploration up to 30 days after surgery.
Safety Assessments:	Safety assessments will include evaluation of the frequency and nature of adverse events (AEs) and adverse device effects (ADEs) up to 30 days after treatment application.
Statistical Analyses:	**Sample Size** A non-inferiority comparison will be performed to determine if the hazard ratio with an overall sample size of 212 subjects (106 HemoStyp group and 106 Surgicel group) achieves 80% power at a 0.05 significance level when the hazard ratio is actually 1.33 (median survival is 3.0 minutes for HemoStyp and 4.0 minutes for Surgicel). The non-inferiority ratio is 0.75 (corresponding to margin of 1 minute). It is anticipated that the proportion of subjects observed with the event during the study is 0.90 for the HemoStyp group and 0.92 for the Surgicel group. These results assume that the hazard ratio is constant throughout the study and that Cox proportional hazards regression or the non-inferiority log-rank test is used to analyze the data. It is anticipated that approximately 710 subjects will be screened to randomize approximately 234 subjects with an anticipated drop-out rate of approximately 10%.

Efficacy Analyses

Analysis of Primary Endpoint

The time to hemostasis will be measured from start of study treatment to the achievement of hemostasis at the target bleeding site (TBS), or to the end of the 10-minute observation period. The time to hemostasis will be considered as censored at the end of the 10-minute observation period. Time to hemostasis will be quantified in minutes according to its nominal time point. When re-bleeding occurs, and the cessation of bleeding is again achieved at a later time point, the effective time to hemostasis will be the latter time point. The time to hemostasis will be the time from start of study treatment to that last effective hemostatic time point.

The primary endpoint analyses will be based on Intent-to-Treat (ITT) population. The primary analysis is the test of non-inferiority of HemoStyp compared with Surgical. The primary endpoint will be tested using Cox proportional hazards regression. The primary endpoint will be tested for superiority after the secondary endpoints have been analyzed. The primary endpoint analyses will also be performed on the Per Protocol (PP) population.

Analysis of Secondary Endpoint

A two-sided z-test with pooled variance will be used to test the difference for each secondary endpoint. The 95% confidence intervals (CIs) for each secondary endpoint in each group (HemoStyp or Surgicel) will be provided. The secondary endpoints will be assessed at the significant level of 0.05 in a defined order after achievement of a significant result for the primary endpoint .

To assess homogeneity of treatment effectiveness, subgroup analyses will be performed.

Interim Analysis

After 118 randomized subjects have been seen at 30 day visit.

Safety Analyses

Safety analysis will be performed on the safety population using descriptive statistics without inferential tests for significance. Safety evaluation will include monitoring of adverse events (adverse events/serious adverse events [SAEs]) and adverse device effects (ADEs). Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events will be presented in summary tables by system organ class (SOC), preferred term and by treatment group. The number and percentage of subjects within each SOC and preferred term and the number of adverse events within each SOC and preferred term will be presented. The summary of adverse events by severity will be tabulated. The summary of adverse events by causality will also be provided. For each patient and each adverse event, the worst severity and causality recorded will be used in the by-intensity and by-relationship summaries.

Table 1.1 Schedule of Evaluations

	Screening	Surgery	Post-surgical Follow Up
Visit	V1	(Randomization) V2	V3
Trial Day	Day -10 to 0	Day 0	Day 30 ± 7
Informed consent	X		
Inclusion / Exclusion criteria	X	X	
Demographics	X		
Medical history	X		
Concomitant medication review	X	X	X
Vital signs	X		
Height and Weight	X		
Laboratory Measures[1]	X		
Urine pregnancy test[2]	X		
Surgery performed		X	
Appropriate target bleeding sites identified[3]		X	
Randomization		X	
Treatment applied to target bleeding sites		X	
Time to hemostasis of target bleeding sites		X	
Assess for re-bleeding or post-surgical re-bleeding		X----------X	
Adverse events review		X	X

1. Laboratory parameters obtained for subjects as pre-operation standard of care that include a complete blood count (CBC) and may include prothrombin time (PT) and partial thromboplastin time (PTT) reflecting patients medical and medication history.
2. Obtained for women of child-bearing potential.
3. Appropriate target bleeding sites are defined as having a Bleeding Severity Scale Grade of 1 (Mild) or 2 (Moderate) (Lewis 2017).

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LIST OF ABBREVIATIONS

AE	Adverse Effect
ADE	Adverse Device Effect
ANOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CBC	Complete Blood Count
DIC	Disseminated Intravascular Coagulation
DSMB	Data Safety Monitoring Board
IEC	Independent Ethics Committee
eCRF	Electronic Case Report Form
EEA	European Economic Area
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention-To-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
ORC	Oxidized Regenerated Cellulose
PI	Primary Investigator
PTT	Partial Thromboplastin Time
PT	Prothrombin Time
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TBS	Target Bleeding Site
UADE	Unanticipated Adverse Device Effect
WOCBP	Woman of Childbearing Potential

2 INTRODUCTION

Topical agents have been used to facilitate hemostasis for thousands of years, but remained largely ineffective in practice until the past century.[1] Advances in hemostatic technology have led to an assortment of products in the market today that are all capable of controlling bleeding. Topical hemostats are invaluable in surgery to control bleeding when conventional hemostatic methods such as ligature or cautery are impractical or ineffective. They were used in approximately 30% of surgical procedures in 2010[2], and that number continues to rise.

Choosing an adjunctive hemostatic agent not only requires evaluation of the situation in which a product will be applied, but also consideration of the product's efficacy, safety, ease of use, and affordability. In most cases, bioabsorbable hemostats are more desirable than non-absorbable hemostats because they do not have to be removed from the wound, which often results in re-bleeding. This is especially true for intraoperative use, where the consequences of re-bleeding are more severe, and it is much easier and safer to leave the hemostat on the wound to eventually be absorbed by the body.

HemoStyp (United Health Products, Inc.) is a patented bioabsorbable hemostatic gauze made from oxidized regenerated cellulose (ORC). Various forms of oxidized regenerated cellulose gauze have been available since 1942. The cellulose is obtained from cotton viscose and chemically treated to make it bioabsorbable, resulting in oxidized derivatized esterified cellulose. The end product is all natural, with no harmful chemicals or animal byproducts. It is a Class II medical device registered with the FDA to control bleeding in open wounds and in body cavities. Hemostyp is a sterile, woven, pH neutral gauze consisting of oxidized, esterified cellulose that is hypoallergenic and 100% water soluble. It is applied dry and as it absorbs blood it promptly turns into a gel, plugging the wound and providing a scaffold for the natural clotting process. The gel quickly dissolves into glucose and saline which is then harmlessly and easily absorbed by the body. It does not have to be removed from the wound. Any residue is easily removed with saline or can be left in the wound site to be absorbed.

Extensive research and laboratory testing has shown that Hemostyp is completely safe. pH testing was performed in January 2018 demonstrated a pH of 7.21. (reference—data on file) Dissolution studies have demonstrated that Hemostyp begins to dissolve in water within 1 minute and has total dissolution within 24 hours. (reference- data on file). Hemostyp is sterilized by radiation using conditions validated following ISO 11137-2: 2006'(ref data on file). Bioburden testing demonstrated an estimated burden of 43 cfu/unit. (ref data on file)

Additionally, in long-term animal studies of 3 weeks, necropsy results show that no Hemostyp was visible at the vessel site or under the skin, and the surrounding tissue appeared normal. The histopathology results showed an absence of neutrophils and a relatively quiescent leukocyte response in the tissues where Hemostyp was placed, indicating that the gauze was not contaminated with bacteria and that the immune response to the gauze was of minimal severity. Overall, Hemostyp performed as postulated, providing a lattice/scaffold to assist in clot formation and then being completely broken down and removed by the bodies systems without apparent harm (ref: data on file).

HemoStyp Mechanism of Action

The body relies on several mechanisms to achieve hemostasis. The first is primary hemostasis, that consists of vasoconstriction, which is the body's first response to injury in the vascular wall. When injury occurs, vessel walls constrict, causing reduced blood flow to the site of injury. HemoStyp enhances this recruiting process by absorbing water and other fluids from blood, making it viscous and slower moving, which also helps to minimize blood loss. Unlike most absorbable hemostats, HemoStyp is capable of increasing the viscosity of blood even in situations complicated by coagulation pathology or the use of anticoagulation drugs. This was demonstrated in an experiment in which HemoStyp initiated clotting in heparinized rabbit blood.[2]

The second method of primary hemostasis is platelet aggregation with the formation of a platelet plug. HemoStyp Hemostatic Gauze expedites hemostasis by creating an artificial clot that facilitates the natural blood clotting process. As it expands, it absorbs blood, entrapping blood proteins, platelets, and cells, essentially providing a scaffold for the natural clotting process. While this is happening, the gauze fibers begin to turn into a gel that plugs the wound, preventing further blood loss and providing a surface for platelet aggregation followed by solid fibrin clot formation.

Almost immediately after a blood vessel sustains an injury, platelets in the blood become activated, releasing chemicals that promote adhesion to other platelets and to blood vessel linings so that a platelet plug can be formed at the wound site. As such, the initial solid fabric state of HemoStyp gauze increases platelet aggregation at the wound site, expediting the formation of a platelet plug.

This is followed by secondary hemostasis. When bleeding is from larger vessels, blood clot formation is required. For blood coagulation to occur, the platelet plug is replaced with a stronger blood clot through a series of interdependent, enzyme-mediated reactions that bring about the generation of thrombin and the formation of fibrin from fibrinogen. This is accomplished through the intrinsic and extrinsic pathways. The intrinsic pathway starts with the conversion of clotting factor XII to its enzymatically active form, which is accomplished through contact with certain negatively charged surfaces. The negatively charged surface of HemoStyp ORC activates factor XII and initiates the intrinsic pathway of blood coagulation, leading to the formation of fibrin and thus enhancing another component of the hemostatic process. The activity of the intrinsic pathway can be measured by the partial thromboplastin test (PTT).

Hemostatic Efficacy

Research to date, has demonstrated the efficacy of HemoStyp Hemostatic Gauze in accelerating hemostasis. The PTT and the prothrombin time test (PT) measure the effectiveness of the intrinsic and extrinsic coagulation pathways, respectively. Blood mixed with HemoStyp was found to have significantly accelerated PTT and PT values, thus indicating its activity in enhancing both pathways.[3-4] Additionally, HemoStyp gauze was able to achieve hemostasis in multiple studies in which the femoral artery was lacerated in a swine model.[5-6] Swine are useful models because their cardiovascular systems are quite similar to

human's. As such, a laceration to the femoral artery, one of the largest vessels in the human and porcine body, is unable to produce hemostasis naturally before too much blood is lost. HemoStyp gauze achieved hemostasis consistently before fatal amounts of blood were lost, further demonstrating its efficacy.

Animal model research has shown that HemoStyp Hemostatic Gauze is equally or more effective than other available hemostats and current standard of care. One femoral artery study done in an animal model was a comparison to surgical lap sponges (non-absorbable gauze pads), and HemoStyp achieved hemostasis in significantly more swine.[5] Another experiment found HemoStyp to be equally as effective in achieving hemostasis as Bloodstop (Lifescience), a more expensive type of ORC hemostat, in body surface and liver wounds in a rabbit model.[2] In vitro, HemoStyp was also found to have faster clotting times in a PT comparison to Surgicel® (Johnson & Johnson) the main commercial ORC in use today.[4] HemoStyp also had faster clotting times in a PT comparison to Gelfoam (Pfizer) as well, which is a widely used gelatin-based hemostat made from porcine skin.[4]

Purpose of the Study

The purpose of this study is to demonstrate efficacy in the intra-operative setting in order to apply to the FDA for PMA Class III approval, which will allow HemoStyp to be used for intraoperative bleeding. HemoStyp recently obtained Class III and CE mark approval in the European Economic Area (EEA). This study is designed to evaluate the efficacy and safety of HemoStyp hemostatic gauze compared with Surgicel for the treatment of mild to moderate bleeding that arises during several types of surgery including general, cardio-thoracic, and vascular surgeries.. This study will use a validated bleeding severity scale that fulfills the FDA's requirements for a clinician-reported scale. [8]

Another study evaluated the time to hemostasis using HemoStyp in a swine liver punch model. Five Landrace X Yorkshire X Duroc crossbred healthy pigs were tested. After exposure of the liver, a 6 mm diameter biopsy punch by 7 mm depth lesion was created and the core was elevated with thumb forceps and cut with a # 15 blade. Dry gauze was immediately placed on the defect for a few seconds, upon removal, the HemoStyp was placed into and over the defect and wet (0.9% sodium chloride) gauze placed on the HemoStyp with mild pressure for 2.5 minutes. If hemostasis was not achieved, the dry gauze, HemoStyp with wet gauze cycle was repeated and time was recorded at 2.5, 5, and 10-minute increments for hemostasis. Five sites/insults were created and recorded for each animal. After 30 minutes post creation of the final punch, the animals were euthanized. The study results included all lesions with HemoStyp achieved hemostasis within the 10-minute limit. Almost all punch sites achieved hemostasis within the 2.5-minute range, and those that did not were due to surgeon error. All 20 defects achieved hemostasis with reapplication of HemoStyp. Results of this study suggest that properly placed HemoStyp will achieve hemostasis in liver tissue within 2.5 minutes for this type of lesion.[9]

3 STUDY OBJECTIVES

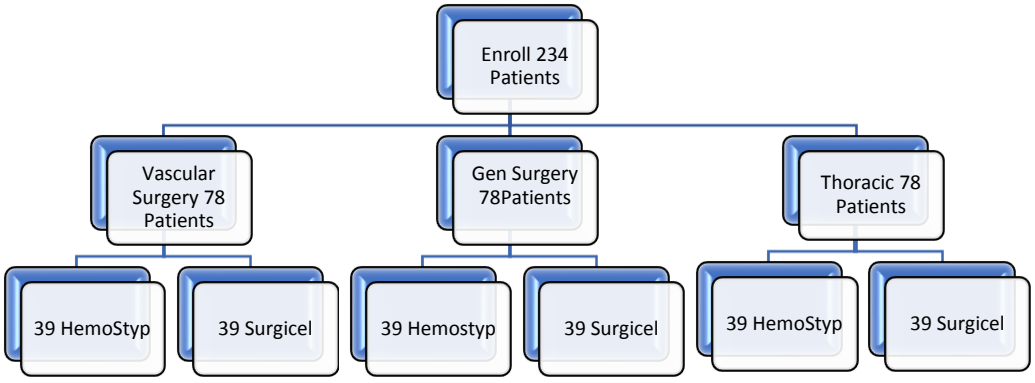
To assess efficacy and safety of HemoStyp as an adjunct for management of secondary hemostasis in the operative setting.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This study is a prospective, non-inferiority, multicenter, randomized, open-label trial to compare HemoStyp with Surgicel in the management of bleeding during surgeries.

Approximately 234 subjects will be randomized in a 1:1 ratio to either HemoStyp or Surgicel. Treatment randomization will be stratified by study centers and generated prior to study initiation. It is anticipated that approximately 710 subjects will be screened to enroll approximately 236 subjects with an anticipated drop-out rate of approximately 10%.



4.1.1 Randomization

Randomization will be assigned using sealed envelopes for each arm and each study center.

4.1.2 Scientific Rationale for Study Design

This is a multi-center, open-blind study assigned randomly to 2 treatments (HemoStyp or Surgicel) in a 1:1 ratio. This study is designed to compare HemoStyp with Surgicel, which represents the current standard of care for control of mild to moderate bleeding in an intra-operative setting.

The primary outcome measure for this study is the median time to achieve hemostasis. This is a clinically appropriate outcome measurement in a surgical setting and will assess the whether HemoStyp is non-inferior to Surgicel in terms of the key parameter of median time to achieve hemostasis at target bleeding sites. This study will also evaluate the categorical parameters, namely the percentage of subjects achieving hemostasis at pre-specified time intervals (30 second intervals from application through 10 minutes). In addition, this study appropriately evaluates the percentage of subjects with re-bleeding events during surgery and any post-surgical events requiring additional surgery during a 30-day follow-up period.

4.1.3 End of Study Definition

A participant is considered to have completed the study if he/she has completed the surgery and follow-up visit shown in Table 1.1 Schedule of Evaluations. The end of the study is

defined as the date of the last scheduled procedure was performed for the last participant in the trial.

5 STUDY ENDPOINTS

5.1 Primary Endpoint

The primary performance endpoints include:

- Time to hemostasis from start of study treatment at target bleeding site until 10 minutes after treatment initiation.

5.2 Secondary Endpoints

Secondary efficacy endpoints include:

- Percentage of subjects achieving hemostasis at the target bleeding site at 2 minutes, 5 minutes and 10 minutes following the start of study treatment;
- Percentage of subjects with intraoperative hemostasis at the target bleeding site;
- Percentage of subjects with intraoperative re-bleeding from the target bleeding site post hemostasis; and
- Postoperative re-bleeding from the target bleeding site requiring surgical re-exploration up to 30 days after surgery.

5.3 Safety Assessments

Safety assessments will include evaluation of the frequency and nature of adverse events (AEs) and adverse device effects (ADEs) up to 30 days after treatment application.

6 SELECTION OF STUDY POPULATION

6.1 Inclusion Criteria

Subjects will be eligible to participate in this study if they meet all of the following criteria:

1. Elective procedure (non-laparoscopic thoracic, abdominal, or vascular surgery);
2. At time of surgery has mild to moderate soft tissue, vascular or parenchymal bleeding present at target bleeding site after primary standard conventional surgical hemostatic methods are proven to be ineffective or impractical;
3. Ages: Adult subjects ≥18 years of age; and
4. Subjects who are willing and able to sign consent.

6.2 Exclusion Criteria

Subjects will not be eligible to participate in this study if they meet any of the following criteria:

1. Physical or psychological condition which would impair study participation;
2. Indications for emergency surgery;

3. Pre-operative laboratory findings of a hematologic disorder;
4. Subjects with history of moderate to severe allergies;
5. Subjects undergoing minimally invasive laparoscopic surgery;
6. Subjects who will require platelet or fresh frozen plasma transfusion during surgery;
7. Subjects who are pregnant or breast-feeding at the time of surgery; or
8. Subjects on P2Y12 platelet inhibitor (Plavix) less than 5 days prior to surgery, warfarin or Xa inhibitors not withheld per standard protocols for the management of anticoagulants pre-operatively.
9. Patients with a coagulation disorder, thrombocytopenia, liver disease and anti-thrombin therapy.

6.3 Screen Failures

All subjects signing the informed consent who do not have mild to moderate soft tissue, vascular or parenchymal bleeding (based on validated scale [Lewis 2017]) present at target bleeding site after primary standard conventional surgical hemostatic will be recorded as screen failures. The relevant electronic Case Report Form (eCRF) pages (demographics, reason for screen failure) will be completed for all screen failure subjects and the data will be included in the study database.

6.4 Removal of Subjects from Study

In accordance with the current revision of the Declaration of Helsinki and the Code of Federal Regulations, a subject has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or the institution. Should a subject (or subject's legally authorized guardian/representative) decide to withdraw; all efforts will be made to collect any adverse events they have experienced, if applicable. Subjects who withdraw or are terminated early from the study may be replaced. Participation may be terminated prior to completing the study for any of the reasons listed below (reasons that do not fit the categories below will be documented as "other").

Withdrawal of Consent:

If a subject chooses to withdraw early from the study, the eCRF completion page should be completed. When a subject's participation is terminated prior to completing the study, the reason for withdrawal is to be documented on the eCRF and in the source documentation.

Surgical:

The Investigator must withdraw a subject intraoperatively for the following reasons:

- Subjects do not have an appropriate target bleeding site.
- Subject develops coagulation diathesis post-operatively such as DIC (Disseminated Intravascular Coagulation).

Death:

When possible, the cause of death will be documented.

Lost to Follow-up:

All subjects should be encouraged to return for protocol required clinic visits for evaluation during the study follow-up period. If a patient is unable to return for a clinic visit or unable to be contacted by telephone, attempts to contact the patient should be documented in the source documents. Only after failing to contact the patient at the final follow-up visit, the patient will be considered lost to follow-up and the primary reason for early termination will be completed in the eCRF.

Site Termination or Study Termination:

The Sponsor may terminate a site or study at any time. When this occurs all subjects at the site will be withdrawn and documented as early termination. Reasons for site or study termination may include, but are not limited, to the following:

- Administrative concerns (e.g., inadequate patient enrollment, investigator/institution non-compliance, change of business strategy, etc.).
- Safety issues, including reaching any of the complication thresholds, including those due to non-compliance, which substantially affect the risk-to-benefit ratio of the study subjects at a site or for the study as a whole.
- Futility: It is evident that the endpoint cannot be reached given the trial design and number of enrolled participants.
- Regulatory body mandates.

The Investigator has the right to terminate their participation at any time. Should this be necessary, procedures for termination will be provided by the Sponsor.

7 STUDY PROCEDURES BY VISIT

Surgical procedures will be performed according to the expected standard of care and practices guided by the surgical specialty guidelines and institutional SOPs. Primary hemostasis of major bleeding should be achieved with conventional methods (i.e., clips, cautery, sutures). Subjects with an appropriate target bleeding site will allow the subject to be randomized into the study treatment. Each treatment will be applied in accordance with technical instructions provided in the investigator manual. Upon application of the study treatment at target bleeding site, a stopwatch will be started with inspection for bleeding occurring every 30 seconds for 10 minutes. In addition, the investigator will inspect the target bleeding site for 5 minutes after hemostasis is presumed to be achieved to ensure rebleeding does not occur.

All procedures will occur within the time windows defined in the study visit Schedule of Evaluations (see in Table 1.1).

7.1 Screening: Day -10 to Day 0 (Visit 1)

At the pre-operative visit, the physician will discuss with the patient the potential use of the investigational product, HemoStyp versus the standard of care product Surgicel, for secondary hemostasis. The physician performed the following procedures:

- Obtain written informed consent before any study-related procedures are conducted;
- Review of inclusion and exclusion criteria;
- Collect demographics data including age, sex, and race/ethnicity;
- Review medical history;
- Review and record concomitant medications (including any medication taken within 30 days of the screening visit);
- Record height and weight;
- Urine pregnancy test
- Measure vital signs (heart rate, respiratory rate, and blood pressure only);
- Laboratory tests (within 30 days prior to the screening visit). If these tests based on standard of care were done within 30 days prior to the screening visit date, these tests do not need to be repeated at the screening visit. The tests are, as follows:
    - Complete blood count (CBC), including hemoglobin, hematocrit, and platelet count; and
    - Coagulation tests, may include prothrombin (PT) and partial thromboplastin time (PTT) and International Normalized Ratio (INR) reflecting patients medical and medication history.

7.2 Study Treatment Day 0 (Visit 2 – Surgery)

On Day 1, eligible subjects will report to the hospital/surgical site at the scheduled time. Prior to surgery, the following procedures will be performed:

- Review of inclusion and exclusion criteria; and
- Review and record any changes to concomitant medications.

Other procedures will be performed in accordance with the pre-surgical and surgical site standards.

During the surgical procedure, subjects with appropriate target bleed sites (TBS) as determined using the validated bleeding severity scale (see Section 8.6) will be randomized to their assigned treatment (HemoStyp or Surgicel).

Each treatment will be applied in accordance with technical instructions provided in the investigator manual. Upon application of the study treatment at target bleeding site, a stopwatch will be started with inspection for bleeding occurring every 30 seconds for 10 minutes. In addition, the investigator will inspect the target bleeding site for 5 minutes after hemostasis is presumed to be achieved to ensure rebleeding does not occur.

7.3 Day 30 ± 7 (Visit 3)

From Day 0 through Day 30, subjects will be carefully monitored for any re-bleeding or need for exploratory surgery at the surgical site due to re-bleeding episodes. Any events of re-bleeding and/or requirement for additional surgery to address bleeding will be recorded and completely described.

On Day 30, subjects will report to the clinical for the follow-up procedures:

- Review and record concomitant medication;
- Assess for any re-bleeding at the target site; and
- Assess and record any adverse events or any adverse device reactions.

Following this, participation in the study will be completed.

8 STUDY PROCEDURES

8.1 Informed Consent

Adult Subjects

Each subject must sign and date a study specific ICF. The consent form will comply with all applicable regulations governing the protection of human subjects. An ICF approved by the Sponsor must be used.

The Investigator will obtain Institutional Review Board (IRB) written approval of the ICF to be provided to the subjects, including IRB approval of all revisions. Prior to entering the study, the Investigator or an authorized staff member will inform subjects about the nature of the study. Subjects will have the opportunity to inquire about details of the study and to decide whether to participate.

The Investigator will provide each subject with a copy of the signed and dated ICF and will document in the subject's source notes that informed consent was given.

8.2 Medical History

At the Screening Visit, a complete medical history will be obtained from each subject. The medical history will assess the subject for any disqualifying medical conditions as specified in the inclusion and exclusion criteria. The medical history will include all currently relevant history. When possible, only diagnoses and surgeries will be recorded. It is not necessary to collect history for remote, resolved conditions such as past pediatric illnesses or surgeries, unless the examining physician deems these conditions relevant.

8.3 Concomitant Medications

At the Screening and Randomization (Day 0) Visits, a list of all currently used medications will be obtained from each subject.

8.4 Height and Weight

The subject's height (cm or in) and weight (kg or lb) will be measured at the Screening Visit.

8.5 Vital Signs

Vital signs (heart rate, blood pressure, and temperature) will be assessed at the Screening Visit.

8.6 Laboratory Assessments

The investigator will review the laboratory report, document this review, and determine eligibility of the subject based on the laboratory findings.

8.7 Assessment of Target Bleeding Sites

During the surgical procedure on Day 1, appropriate target bleed sites will be identified, characterized, and recorded on the eCRF.

A specific bleeding area/site will be defined as the target bleeding site (TBS) when it is determined by the investigator that control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) is ineffective or impractical and will require an adjunct treatment to achieve hemostasis. When the TBS is identified, the investigator will rate the intensity of the bleeding at the TBS according to the validated bleeding scale (Lewis 2017) shown in the table below. Only subjects with a TBS qualitative description of mild or moderate severity will be randomized.

The surgical raters used for intraoperative recruitment of patients will be trained on a video library of different bleeding rates. These videos will be verified with gravimetric measurements of blood loss. Inter- and Intra-rater reliability will be assessed prior to protocol participation. Inter- and Intra-rater concordance should exceed 90% for a bleeding grade of "0" or hemostasis and a bleeding grade of "3" or severe bleeding.

Validated Bleeding Severity Scale

Grade	Visual presentation	Anatomic appearance	Qualitative description	Visually estimated rate of blood loss (mL/min
0	No bleeding	No bleeding	No bleeding	≤1.0
1	Ooze or intermittent flow	Capillary-like bleeding	Mild	>1.0-5.0
2	Continuous flow	Venule and arteriolar-like bleeding	Moderate	>5.0-10.0
3	Controllable spurting and/or overwhelming flow	Noncentral venous- and arterial-like bleeding	Severe	>10.0-50.0
4	Unidentified or inaccessible spurting or gush	Central arterial- or venous-like bleeding	Life threatening*	>50.0

* Systemic resuscitation is required (e.g., volume expanders, vasopressors, blood products, etc.).
The scale is designed and validated for use in clinical studies to generate labeling claims. The scale is a Likert-type scale, in which the user assigns a grade based on the overall agreement of the items listed.
Source: Lewis 2017

Upon application of the study treatment at target bleeding site, a stopwatch will be started with inspection for bleeding occurring every 30 seconds for 10 minutes. In addition, the investigator will inspect the target bleeding site for 5 minutes after hemostasis is presumed to be achieved to ensure rebleeding does not occur. The source of the TBS will be identified and recorded as arterial, venous, or capillary.

8.8 Length of Hospital Stay

The length of the hospital and intensive care stay (if applicable) will be captured.

9 ADVERSE EVENTS

9.1 Definitions

Adverse Event

For this study, an adverse event is defined as any undesirable clinical occurrence in a patient that may be attributable to the study procedure or device.

Serious Adverse Event (SAE)

A serious adverse event (SAE) is an adverse event that results in one or more of the following for this study:

- Death;
- Life-threatening: life-threatening means that the subject was at immediate risk of death from the reaction as it occurred;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions;
- Is a congenital anomaly or birth defect; or
- Is an important medical event, based upon appropriate medical judgment, and may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above (e.g. death, life-threatening, hospitalization, etc.).

Unanticipated Adverse Device Effect (UADE)

Unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Associated with the investigational device: There is a reasonable possibility that the adverse effect may have been caused by the investigational device.

Life-threatening adverse effect: Any adverse effect that places the subject, in the view of either the investigator or the sponsor, at immediate risk of death from the effect **as it occurred**. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse effect: An adverse effect is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of outcomes described in the definition of SAE (see definition of SAE above).

Unanticipated adverse effect: Any adverse effect, the nature, specificity, severity, or frequency of which is not consistent with the risk information in the clinical study protocol or elsewhere in the current IDE application.

9.2 Collection of Adverse Events and Adverse Effect Information

All adverse events and adverse effects, serious and non-serious, will be collected from the time a subject signs the informed consent through the last study visit. Clinical study subjects will be routinely questioned about adverse effects at study visits.

9.3 Management of Adverse Events

The Investigator will manage each adverse event/adverse effects in accordance with accepted standards of medical care, with primary attention to the well-being of the subject. To the extent appropriately possible, achievement of study objectives will be considered. The investigator will arrange for provision of care by other professionals (e.g., emergency service providers, hospital, and consulting specialist) as needed.

9.4 Recording and Assessment of Adverse Effects

All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of treatment group, if applicable, or suspected causal relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s) will be recorded in the subjects' case histories (eCRF). For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a *serious adverse effect*) and; 2) an assessment of the casual relationship between the adverse effect and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Adverse effects or abnormal test findings felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the sponsor-investigator.

9.5 Abnormal Test Findings

An abnormal test finding will be classified as an *adverse effect* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms;

- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug or other therapy (Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse effect.);
- The test finding leads to a change in study treatment or exposure or discontinuation of subject participation in the clinical study; or
- The test finding is considered an adverse effect by the sponsor-investigator.

9.6 Adverse Event Severity

The investigator is responsible for assessing the severity of an adverse event. A change in severity may constitute a new reportable adverse event. The following guideline should be used to determine the severity of each adverse event:

- Mild: Awareness of signs or symptoms, but does not interfere with the patient's usual activity, or is a transient event that resolves without treatment and with no sequelae.
- Moderate: Discomfort enough to cause a noticeable impact on the subject's daily life.
- Severe: Incapacitation or significant impact on the subject's daily life.

9.7 Adverse Event Causality

It is the Investigator's responsibility to assess the relationship between all adverse events and the study procedure. Only adverse events attributable (relationship of possibly, related, or unknown) to a device or the study procedure are to be recorded in the eCRF.

- Possibly: A clinical event (including abnormal laboratory result) that presents an unlikely association between device/procedure, which cannot be ruled out with certainty, but could also be explained by alternative etiology.
- Related: A clinical event (including abnormal laboratory result) that presents a strong temporal relationship between device/procedure, in which an alternative etiology is unlikely.
- Unknown: A clinical event (including abnormal laboratory result) that cannot be determined to be related or unrelated to device/procedure given the information obtained.

9.8 Reporting Adverse Events

The Investigator is required to report all adverse events experienced by the patient from the day of the surgical procedure (Visit 2) until the patient completes Visit 3 (30 days after the surgical procedure) or withdraws early (prior to Visit 3). All adverse events (both serious and non-serious), regardless of their relatedness to the study device or procedure, must be reported in the Adverse Event eCRF. The investigator will evaluate the severity of the event, and its relatedness to the study device or procedure. Both severity and relatedness of all adverse events need to be entered in the Adverse Event eCRF.

Any necessary medical management of the event will be recorded in the patient's medical record/source document. All adverse events must be followed until resolution or until they become stable but ongoing.

The Investigator will record all adverse events (both serious and non-serious) in the source documents. Standard medical terminology should be used when recording adverse events. 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 adverse event to the device used in the study
- Relationship of the adverse event to the study surgical procedure
- Indication of whether the event is serious.

Data related to SAEs will be collected until event resolution, or until the event is considered stable, or until all attempts to determine the resolution of the event are exhausted. All adverse events that are unresolved at study completion (or early termination) will be recorded as ongoing at study end.

9.8.1 Procedures for Reporting Serious Adverse Events to the Sponsor

All SAEs that occur during the course of the study regardless of causality must be reported by the Investigator **within 24 hours** from the point in time when the Investigator becomes aware of the SAE. The SAE form should be submitted to the study medical monitor.

All serious adverse events, regardless of causality, should be collected and reported beginning with signing of the ICF through the follow-up visit.

Any SAEs that occur after the End of Study Follow-up Visit has concluded, including after the study has concluded, and that are **considered related to the study device or procedure by the Investigator** are considered reportable, and must be reported to the Sponsor **within 24 hours**.

The information collected by the site will include a minimum of the following: subject number; a thorough description (narrative) of the event, including its onset, relevant signs/symptoms, progression, treatment and outcome; and an assessment by the Investigator as to the severity of the event and relatedness to any/all study device(s) or study procedure(s).

The information reported on the SAEs report form should match the data provided by the site on the eCRF. The Investigator is also responsible for spontaneously reporting any subsequent follow-up information, including clinically relevant additional information, such as change in outcome.

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

9.8.2 Procedures for Reporting Unanticipated Adverse Device Effects

Reporting UADEs to the Sponsor

The study site must report all SAEs, whether they are related to the device or procedure, to the Sponsor as soon as possible, but no later 24 hours of becoming aware of the SAE.

Information not available at the time of the initial report (e.g., an end date for the UADE) must be updated within the safety database. 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 patient.

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 and FDA approval.

Reporting UADEs to the FDA

For any observed or volunteered adverse event that is determined to be a UADE, the sponsor-investigator will submit an expedited safety report to the FDA's Center for Devices and Radiological Health. The expedited safety report will consist of:

- a completed Form FDA 3500A
- a cover letter analyzing the significance of the event

A copy of this safety report will be provided to all participating study investigators.

The completed Form FDA 3500A and cover letter will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the sponsor-investigator first receives notice of the adverse effect.

If, following receipt and investigation of follow-up information regarding an adverse effect that was previously determined not to be a UADE, the sponsor-investigator determines that the event does meet the requirements for expedited reporting, the sponsor-investigator will submit a completed Form FDA 3500A and cover letter as soon as possible, but in no event later than 10 working days, after the determination is made.

Subsequent to the initial submission of a completed FDA Form 3500A, the sponsor-investigator will submit additional information concerning the reported adverse effect as requested by the FDA.

Reporting Adverse Effects to the IRB

For any adverse event determined to be a UADE, the sponsor-investigator will submit the completed Form FDA 3500A and cover letter to the IRB as soon as possible and, in no event, later than 10 working days after the sponsor-investigator first receives notice of the adverse effect.

Follow-up information to reported adverse effects will be submitted to the IRB as soon as the relevant information is available.

9.8.3 Reporting of Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until last study visit.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Monitoring

Study progress will be monitored by United Health Products or its representative as frequently as necessary to ensure adequate and accurate data collection, protocol compliance and to determine that the study is being conducted in conformance with accepted regulatory requirements. Arrangements for monitoring visits will be made in advance, except in case of emergency. Details will be provided in the study specific Monitoring Plan.

10.2 Study Audit

The study may be audited to assess adherence to the Study Protocol. The consistency of the data presented in the report will be verified by either the Sponsor or designee. During the conduct of the study, process-related and facility-related audits may be performed as well. The clinical research site will be monitored by the study monitor to ensure correct performance of the study procedures and ensure that the study is conducted according to the relevant regulatory requirements. Electronic CRF entries will be verified with the source documentation, if applicable. In some cases, there are no source pages; therefore, verification is not necessary.

Regulatory authorities, the IRB, the Sponsor's quality assurance group, or all parties may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator,

who must provide support at all times for these activities. Quality control principles will be applied throughout the performance of this study.

11 STATISTICAL AND ANALYTICAL PLANS

A detailed Statistical Analysis Plan (SAP) will be written and approved prior to database lock. The SAP will describe all planned analyses based on the statistical design of this study and the subsequent data collected. A brief overview of key statistical analyses is provided below.

11.1 Determination of Sample Size

A non-inferiority comparison will be performed to determine if the hazard ratio with an overall sample size of 212 subjects (106 HemoStyp group and 106 Surgicel group) achieves 80% power at a 0.05 significance level when the hazard ratio is actually 1.33 (median survival is 3.0 minutes for HemoStyp and 4.0 minutes for Surgicel). The non-inferiority ratio is 0.75 (corresponding to margin of 1 minute). It is anticipated that the proportion of subjects observed with the event during the study is 0.90 for the HemoStyp group and 0.92 for the Surgicel group. These results assume that the hazard ratio is constant throughout the study and that Cox proportional hazards regression or the non-inferiority log-rank test is used to analyze the data.

It is anticipated that approximately 710 subjects will be screened to randomize approximately 236 subjects with an anticipated drop-out rate of approximately 10%.

11.2 Analysis to be Conducted

11.2.1 General Conventions

Summary tables (descriptive statistics and/or frequency tables) will be provided for all demographic, baseline variables, efficacy and safety variables by treatment group. Continuous data will be summarized in terms of mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum, maximum and number of valid observations. Categorical data will be summarized in terms of the number of subjects, frequency counts and percentages. All data will also be presented in by-patient listings.

11.2.2 Analysis Populations

Intent-To-Treat Population (ITT): The ITT population will include all subjects who are randomized to HemoStyp or Surgicel. The efficacy analysis will be performed using the ITT population.

The Per Protocol population (PP): The PP population will include all subjects who are not major protocol violators with regards to inclusion/exclusion criteria, randomization, and have availability of scheduled data for all treatments and efficacy evaluations.

Safety Population: The safety population will include all subjects who are treated with any amount of HemoStyp or Surgicel. Safety analyses will be performed using the safety population and subjects will be analyzed according to the treatment they actually receive.

11.2.3 Disposition of Study Subjects

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

11.2.4 Demographic, Baseline, and Clinical Characteristics

Summary statistics will be provided for patient demographics and baseline characteristics by randomized treatment group and in total. These characteristics will be compared between treatment groups using Fisher's Exact test for categorical variables and the two-sample t-test or Wilcoxon Rank Sum test for continuous variables.

11.2.5 Efficacy Analyses

Primary Endpoint

The time to hemostasis will be measured from start of study treatment to the achievement of hemostasis at the target bleeding site (TBS), or to the end of the 10-minute observation period. The time to hemostasis will be considered as censored at the end of the 10-minute observation period. Time to hemostasis will be quantified in minutes according to its nominal time point. When re-bleeding occurs, and the cessation of bleeding is again achieved at a later time point, the effective time to hemostasis will be the latter time point. The time to hemostasis will be the time from start of study treatment to that last effective hemostatic time point.

Secondary Endpoints

- Percentage of subjects achieving hemostasis at the target bleeding site at 2 minutes and at 5 minutes following the start of study treatment;
- Percentage of subjects with intraoperative hemostasis at the target bleeding site;
- Percentage of subjects with intraoperative re-bleeding from the target bleeding site post hemostasis;
- Postoperative re-bleeding from the target bleeding site requiring surgical re-exploration up to 30 days after surgery.

Analysis of the Primary Endpoint

The primary endpoint analyses will be based on ITT population. The primary analysis is the test of non-inferiority of HemoStyp compared with Surgical. Cox proportional hazards regression or log-rank test will be used for the analysis of non-inferiority.

The null hypothesis for the testing of the primary endpoint is described below:

H0: HemoStyp is inferior or worse than Surgicel by more than 1 minute for median survival (HR<0.8);

H1: HemoStyp is inferior to Surgicel by less than 1 minute for median survival (HemoStype is not inferior to Surgicel) (HR>0.8);

If the lower bound 95% confidence interval of HR >0.8, we conclude that HemoStype is not inferior to Surgicel.

The primary endpoint analyses will also be performed on the PP population.

Analyses of Secondary Endpoints

A two-sided z-test with pooled variance will be used to test the difference for each secondary endpoint. The 95% confidence intervals (CIs) for each secondary endpoint in each group (HemoStyp or Surgicel) will be provided.

Secondary endpoints will be assessed at significant level of 0.05 in the order listed below after achievement of a significant result for the primary endpoint:

1) Percentage of subjects achieving hemostasis at the target bleeding site at 3 minutes following the start of study treatment
2) Percentage of subjects with intraoperative hemostasis at the target bleeding site;
3) Percentage of subjects with intraoperative re-bleeding from the target bleeding site post hemostasis;
4) Percentage of subjects with postoperative re-bleeding from the target bleeding site requiring surgical re-exploration up to 30 days after surgery
5) Percentage of subjects achieving hemostasis at the target bleeding site at 5 minutes following the start of study treatment
6) Percentage of subjects achieving hemostasis at the target bleeding site at 10 minutes following the start of study treatment

The null hypothesis for the testing of the secondary endpoints is described below:

H0: $\mu 0 = \mu 1$

H1: $\mu 0 \neq \mu 1$,

$\mu 0$ and $\mu 1$ are the percentages for each of the secondary endpoints in HemoStyp group and Surgicel group, respectively.

Analyses of Subgroups

To assess homogeneity of treatment effectiveness, subgroup analyses will be assessed for the following subgroups with a significance level of 15%:

-

- Male vs. Female
- Groups based on target bleeding sites
- Groups based on types of surgery
- Groups based on Lewis bleeding scale

11.2.6 Safety Analyses

Safety analysis will be performed on the safety population using descriptive statistics without inferential tests for significance. Safety evaluation will include monitoring of adverse events (adverse events/SAEs). Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events will be presented in summary tables by system organ class (SOC), preferred term and by treatment group. The number and percentage of subjects within each SOC and preferred term and the number of adverse events within each SOC and preferred term will be presented. The summary of adverse events by severity (mild, moderate, or severe) will be tabulated. The summary of adverse events by causality (possibly related, related, unknown) will also be provided. For each patient and each adverse event, the worst severity and causality recorded will be used in the by-intensity and by-relationship summaries.

11.2.7 Handling of Missing Data

All analyses will be performed only on subjects undergoing surgical procedures during which treatment (HemoStyp or Surgicel) is applied to target bleeding sites. There will be no imputation of missing data for any parameters or for early terminated subjects.

12 RISK AND BENEFITS OF STUDY

HemoStyp is a patented bioabsorbable hemostatic gauze made from ORC. HemoStyp gauze is applied dry swells slightly as it absorbs blood and rapidly converts into a gel that plugs the wound, eventually dissolving into glucose and saline. There are no known side effects of HemoStyp.

This study may or may not provide any benefits to the patient. However, HemoStyp hemostatic gauze is designed as an adjunct for management of secondary hemostasis in the operative setting and has recently obtained CE mark approval in the EEA.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Informed Consent

Informed consent will be obtained in accordance with the Declaration of Helsinki, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25(a)(b), CFR 50.27, 45 CFR 46.116(a)(b), and CFR Part 56(a)), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Sponsor-Investigator will prepare the ICF and HIPAA authorization and provide the documents to IRB for approval. The written consent document will embody the elements of informed consent as described in the ICH and will also comply with local regulations. The Sponsor-Investigator will retain an IRB-approved copy of the ICF in the study master file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If a subject is unable to sign the ICF and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

13.2 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The protocol and consent form will be reviewed and approved by the IRB of each participating center prior to study initiation. Unanticipated adverse device effects will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the ICF will be in the possession of the Investigator before the study is initiated. The IRB's unconditional approval statement will be transmitted by the Investigator to the Sponsor or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; new information that may affect adversely the safety of the subjects of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

13.3 Ethical Conduct of the Study

The study will be conducted in compliance with the ICH Guideline on GCP.

14 ADMINISTRATIVE CONSIDERATIONS

14.1 Modifications to the Protocol

No modifications to the protocol should be made without the approval of both the Principal Investigator and United Health Products. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (i.e., efficacy assessments) will require IRB/IEC notification prior to implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. United Health Products will submit all protocol modifications to the Food and Drug Administration (FDA).

When circumstances require an immediate departure from procedures set forth in the protocol, the Investigator will contact United Health Products to discuss the planned course of action. If possible, contact should be made prior to the implementation of any changes. Any departures from protocol must be fully documented in the source documentation and in a protocol deviation log.

14.2 Case Report Form Completion

An eCRF will be used to enter all appropriate subject data gathered during the study.

14.3 Access to Records

The Investigator must make the office and/or hospital records of subjects enrolled in this study available for inspection by United Health Products or its representative at the time of each monitoring visit. The records must also be available for inspection, verification and copying, as required by regulations, by officials of the regulatory health authorities (FDA and others). The Investigator must comply with applicable privacy and security laws for use and disclosure of information related to this research set forth in this protocol.

14.4 Subject Privacy

To maintain subject confidentiality, all eCRFs, study reports, and communications relating to the study will identify subjects by initials and assigned subject numbers. As required by federal regulations, the Investigator will allow United Health Products and/or its representatives access to all pertinent medical records in order to allow for the verification of data gathered in the eCRFs and for the review of the data collection process. The FDA (or other regulatory authority) may also request access to all study records, including source documentation for inspection.

As applicable, in accordance with HIPAA and associated privacy regulations, a subject authorization to use personally identifiable health information may be required from each subject prior to research activities. This authorization document must clearly specify what parties will have access to a subject's personal health information, for what purpose and for how long.

14.5 Record Maintenance and Retention

The sponsor-investigator will maintain records in accordance with 21 CFR 812, Subpart G, to include:

- FDA correspondence related to the IDE application and Investigational Plan; including copies of submitted Form FDA 3500A, supplemental IDE applications, current investigator lists, progress reports, notice of device recall or disposition, and failure to obtain informed consent reports
- IRB correspondence (including approval notifications) related to the clinical protocol; including copies of adverse event reports and annual or interim reports
- Current and past versions of the IRB-approved clinical protocol and corresponding IRB-approved consent form(s) and, if applicable, subject recruitment advertisements
- Signed Investigator's Agreements and Certifications of Financial Interests of Clinical Investigators
- Curriculum vitae (sponsor-investigator and clinical protocol sub-investigators)
- Certificates of required training (e.g., human subject protections, Good Clinical Practice, etc.) for sponsor-investigator and listed sub-investigators
- Normal value(s)/range(s) for medical/laboratory/technical procedures or tests included in the clinical protocol
- Laboratory certification information
- Instructions for on-site preparation and handling of the investigational device and/or study treatment or diagnostic product(s), and other study-related materials (i.e., if not addressed in the clinical protocol)
- Decoding procedures for blinded trials (incorporate only if applicable)
- Master randomization list (incorporate only if applicable)
- Signed ICF
- Completed Case Report Forms, signed and dated by sponsor-investigator
- Source Documents or certified copies of Source Documents
- Monitoring visit reports
- Copies of sponsor-investigator correspondence to sub-investigators, including notifications of adverse effect information
- Subject screening and enrollment logs
- Subject identification code list
- Investigational device accountability records, including documentation of device disposal
- Retained biological specimen log (incorporate only if applicable)

- Interim data analysis report(s) (incorporate only if applicable)
- Final clinical study report.

The sponsor-investigator will retain the specified records and reports for up to two years after the marketing application is approved for the investigational device; or, if a marketing application is not submitted or approved for the investigational device, until two years after investigations under the IDE have been discontinued and the FDA so notified.

14.6 Study Termination

For reasonable cause, the Investigator, IRB/IEC, or United Health Products may terminate the study. Conditions that may warrant termination include, but are not limited to:

- Subject or Investigator noncompliance.
- Unsatisfactory subject enrollment.
- Lack of adherence to protocol procedures.
- Lack of evaluable and/or complete data.
- Potentially unacceptable risk to study subjects.
- Decision to modify drug development plan.
- Decision by FDA or other regulatory authority.

Written notification that includes the reason for the protocol termination is required.

14.7 End of the Study

For regulatory purposes, the definition of the end of the study is database lock.

14.8 Confidentiality and privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records of the participants in this study. The clinical study site will permit access to such records.

The study participant’s contact information will be securely stored at clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is collected for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Data Management Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Data Management Center staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the sponsor.

14.9 Clinical monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH CCP, and with applicable regulatory requirement(s).

Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

14.10 Quality assurance and quality control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

14.11 Data handling and record keeping

14.11.1 Data collection and management responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

14.12 Publication policy

All information supplied to the investigator by United Health Products or designee and not previously published, is considered confidential and remains the sole property of United Health Products. The eCRFs also remain the property of United Health Products. The investigator agrees to use this information only for purposes of study execution.

The information developed in this study will be used by United Health Products in connection with the development of HemoStyp, thus may be disclosed only as required to government regulatory agencies.

Publication or other public presentation of data resulting from this study requires prior review and written approval of United Health Products. Abstracts, manuscripts, and presentation materials can only be done by the PI and only with approval from the medical advisory oversight committee for United Health Products.

14.13 Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC and approved by regulatory agencies where appropriate, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB/IEC within five working days. The Sponsor will assure the timely submission of amendments to regulatory authorities.

14.14 References

1. Hardean E. Achneck, MD, Bantayehu Sileshi, MD, Ryan M. Jamiolkowski, BA, David M. Albala, MD, Mark L. Shapiro, MD, and Jeffrey H. Lawson, MD, PhD; A Comprehensive Review of Topical Hemostatic Agents Efficacy and Recommendations for Use. Ann Surg. 2010; 251: 217–228.

2. Wright JD, Ananth CV, Lewin SN, et al. Patterns of use of hemostatic agents in patients undergoing major surgery. J Surg Res. 2014; 186(1): 458–466.

3. Comparison of Hemostyp Hemostatic Gauze to Bloodstop Hemostatic Gauze for Body Surface and Liver Wounds in a Rabbit Model, Final Report. October 13, 2017. WuXi Apptec St. Paul, MN. Report available upon request.

4. Partial Thromboplastin Time Test, Final Report. May 13, 2004. Nelson Laboratories Salt Lake City, UT. Report available upon request.

5. Prothrombin Time Test, Final Report. September 3, 2004. Nelson Laboratories Salt Lake City, UT. Report available upon request.

6. Comparison of Hemostyp Trauma Gauze Hemostatic Dressing to Lap Sponges in a Standard Swine Model of Uncontrolled Hemorrhage, Final Report. January 1, 2015. Spring Valley Laboratories, Inc. Sykesville, MD. Report available upon request.

7. Femoral Artery Hemostatic Gauze Testing, Final Report. February 25, 2015. Mount Sterling Biomedical Willard, UT. Report available upon request.

8. Lewis KM, Li Q, Jones DS, Corrales JD, Du H, Spiess PE, Lo Menzo E, DeAnda A Jr. Development and validation of an intraoperative bleeding severity scale for use in clinical studies of hemostatic agents. Surgery. 2017; 161(3): 771-781.

9. Liver Hemostatic Gauze Testing with Punch Biopsy Sites. MSB 04-18 Final Report. May 17, 2018. Mt. Sterling Biomedical. Report available upon request.

14.15 Addendum 1: Summary of Changes

The original protocol was dated 10 September 2018. Amendment 1 (Version 1.2 Date: 02 July 2019) to the protocol provided clarification of study procedures and minor editorial changes. The following changes of key importance were implemented:

Interim Analysis:

Added: After 118 randomized subjects have been seen at 30 day visit.

Table 1.1:

Laboratory parameters obtained for subjects as pre-operation standard of care that include a complete blood count (CBC), prothrombin time (PT), and partial thromboplastin time (PTT) was changed to: **Laboratory parameters obtained for subjects as pre-operation standard of care that include a complete blood count (CBC) and may include prothrombin time (PT) and partial thromboplastin time (PTT) reflecting patients medical and medication history.**

Inclusion Criteria

Inclusion criteria were modified as follows

- 1.Elective procedure (non-laparoscopic thoracic, ~~cardiac~~, abdominal, or vascular surgery);
- 3.Ages: ~~Pediatric subjects ≥2 to 17 years of age and~~ adult subjects ≥18 years of age; and
- 4.Subjects ~~or parent or legal guardian of the subject~~ who are willing and able to sign consent.)

Statistical Analysis: Sample Size:

Sample size was changed from 236 to 234 throughout protocol

Sample size explanation was updated as follows:

It is anticipated that approximately 710 subjects will be screened to randomize approximately 236 subjects with an anticipated drop-out rate of approximately 10%.

With the omission of pediatric patients the protocol will attempt to equally randomize 54 patients across three surgical areas: Thoracic, abdominal and vascular surgery. Therefore the number randomized to each will increase from 60 to 78 subjects per group then randomizing approximately 29 to HemoStyp and Surgicel respectively.

Section 8.1 Informed consent

The following was deleted:

Pediatric Subjects

No pediatric subjects will be enrolled until a sample of at least 118 adult subjects have been enrolled and randomized in the study.

A waiver of consent will not be sought for this study. The study investigator or coordinator will review all portions of the consent in great detail. Any questions will be addressed prior to asking for a signature. Study staff will emphasize that the parent or legal guardian may continue to ask questions at any time during the study and he/she may withdraw consent at any time. Documented informed consent will be obtained from each potential volunteer's parent or legal guardian. Consent must be documented by the volunteer's parents or legal guardian's dated signature on a Consent Form along with the dated signature of the person conducting the consent discussion. If the volunteer's parent or legal guardian is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterward, the volunteer's parent or legal guardian should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent i.e. study staff personnel. A copy of the signed and dated consent and assent forms will be given to the volunteer's parent or legal guardian before participation in the trial begins. The original signed consent forms will remain in locked, study files and will be available for review at any time.

The initial informed consent form (ICF) and any subsequent revised written ICF, and written information must receive IRB approval in advance of use. The volunteer's parent or legal guardian will be informed in a timely manner if new information becomes available that may be relevant to the volunteer's parent's or legal guardian's willingness to continue participation in the trial. The communication of this information will be documented. The investigator is responsible for ensuring that no subject undergoes any study related examination or activity before that subject and/or legal guardian has given written informed consent to participate in the study. The written consent must be given by the subject and/or the legal guardian of the subject, after detailed information about the study has been given and in accordance with any national provisions on the protection of clinical study subjects. The verbal explanation will cover all the elements specified in the written information provided for the subject.

The investigator or designated personnel will inform the subject and/or legal guardian of the subject of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The subject's legal guardian should be given every opportunity to ask for clarification of any points he/she does not understand and, if necessary, ask for more information. At the end of the interview, the subject's legal guardian will be given time to consider the study, if this is required, or if the subject's legal guardian requests more time. Subjects and/or legal guardians will be required to sign and date the ICF.

After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file for possible inspection by regulatory authorities, the IEC, sponsor, and/or CRO personnel. It should be emphasized to the subject's legal guardian that he/she is at liberty to withdraw from the study at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects' legal guardians who refuse to give written informed consent should not be included. For those subjects whose legal guardians withdraw consent participation in the study should be discontinued.

Section 11.2.5 Efficacy Analyses

Analyses of Subgroups was updated to include:

To assess homogeneity of treatment effectiveness, subgroup analyses will be assessed for the following subgroups with a significance level of 15%:

- ~~Pediatric vs. adult~~
- Male vs. Female
- Groups based on target bleeding sites
- Groups based on types of surgery
- **Groups based on Lewis bleeding scale**