Official Title: A Phase 2, Randomized, Single-Blind, Controlled Trial of Topical Raplixa™ (Fibrin Sealant [Human]) in Intraoperative Surgical Hemostasis in a Pediatric Population

NCT Number: NCT02117349

Document Date: Protocol Version 4: 13-July-2016

CLINICAL STUDY PROTOCOL

A Phase 2, Randomized, Single-Blind, Controlled Trial of Topical Raplixa™ (Fibrin Sealant [Human]) in Intraoperative Surgical Hemostasis in a Pediatric Population

Protocol No.: FC-007

Date of Original Protocol: 31 January 2014

Date of Protocol Amendment 1: 13 March 2014

Date of Protocol Amendment 3: 06 October 2014

Date of Protocol Amendment 4: 13 July 2016

Sponsor
Mallinckrodt Pharmaceuticals
675 McDonnell Boulevard
Hazelwood, MO 63042
United States of America

CORRESPONDING PROTOCOL AND PROTOCOL AMENDMENT VERSION NUMBERS –THE MEDICINES COMPANY/MALLINCKRODT, INC

Medicines Company	MNK Interpretation	Notes
Version 1.0, Protocol Date: 31 January 2014	Original Protocol: 31 January 2014	
Version 2.0, Protocol Date: 13 March 2014	Protocol Amendment 1: 13 March 2014	Additionally issued a document on 23 July 2014 titled "Protocol Administrative Letter"
Version 3.0, 06 October 2014	Protocol Amendment 2: 06 October 2014	
Version 4.0, 17 December 2015	Protocol Amendment 3: 17 December 2015	Protocol submitted to Agency for feedback, no comments received
Version 5.0, 17 July 2016	Protocol Amendment 4: 13 July 2016	Protocol submitted to Agency for feedback, no recommendations for revisions received

PROTOCOL AMENDMENT 4 DATED 13 JULY 2016

SUMMARY OF CHANGES

The intention of this amendment is to address feedback from regulatory agencies and to improve subject enrollment.

1. Sponsor revised to Mallinckrodt Pharmaceuticals and all sponsor contact information updated.
2. Format and content revised globally to provide clarity.
3. Global change in product names: Fibrocaps to Raplixa, Fibrospray delivery device to RaplixaSpray device and all references to F+G were revised to R+G.
4. Revised the primary contact to be the Medical Monitor and moved the contact information for the Safety Physician to the list of additional contacts.
5. Revised the contact information for the Clinical Trial Manager.
6. Revised background information to include an additional product approved for hemostasis in the pediatric population.
7. Added reference to Raplixa® package insert.
8. Reduction in the number of subjects in the study from 108 to 87 subjects.
9. The Evaluable population revised to the ITT Population. The ITT Population was denoted as the primary population for the efficacy analysis. A description of the analysis of the primary endpoint has been added.
10. The safety population modified to be subjects who are exposed to any amount of study drug instead of subjects who received at least one dose of study drug.
11. After simultaneous enrollment of the first 2 older cohorts and a review of their safety information by the Independent Data Monitoring Committee (IDMC), enrollment will then proceed in a sequential manner for the 2 younger cohorts with IDMC approval.
12. Spinal and Renal surgical procedures added as two additional surgical indications in which Raplixa may be evaluated.
13. Added the surgery type of “scoliosis surgery” under the spinal surgery type under the section “Diagnosis and Main Criteria for Selection."
14. Clarified blood products allowed during 24 hours prior to treatment with study drug/product. Subject should not receive any whole blood, fresh frozen plasma (FFP), cryoprecipitate, or platelets within 24 hours prior to study drug. Packed red blood cell (PRBC) transfusions are allowed.
15. Thrombin-containing hemostats (recombinant or human plasma-derived products) may be administered, if needed as part of the tiered approach for rescue treatment to achieve hemostasis
16. Efficacy interim analysis of the data will not be performed.
17. Pregnancy test performed on the day of surgery instead of at baseline.
18. Day 30 blood sample for immunogenicity testing will not be collected in infants less 6 months of age and testing will not be done on any samples from infants less than 6 months of age.
19. Days 60 and 90 evaluations were removed from the study. However, should a subject return to the investigator between Day 30 and Day 90 for a routine follow-up visit (not scheduled for the purpose of the study), the investigator will record any update in the subject’s safety information and report such information to the Sponsor using the data collection forms provided.

20. Added a second data lock date to ensure the capture of safety data from visits after Day 30 but before Day 90.
21. Updated the definition, handling and regulatory reporting for device-associated events to be fully compliant with the current regulations in the US, Europe, and Canada.
22. Removed Appendix A (Package Insert for Gelfoam, Absorbable Gelatin Sponge, USP) from protocol.

PROTOCOL AMENDMENT 3 DATED 6 OCTOBER 2014

SUMMARY OF CHANGES

The following significant changes were made to protocol FC-007 version 2.0. All changes are reflected in version 3.0 of the protocol dated 06-Oct-2014.

Items in *italics* were added, while strikethrough text (i.e., ~~text~~) has been deleted.

1. Additional background information and reference added to support the rationale for revising the approach to subject enrollment. (section:1.1.)

   Although there are physiologic differences in the levels of coagulation & fibrinolytic proteins over the maturation of children compared to adults, near adult levels are achieved by most children by 6 months of age, and these differences, are considered to be physiologic, i.e., something that is normal, not due to anything pathologic nor significant in terms of causing illness (7, 8).
   To date, there are only two fibrin sealants, Recothrom^{R} and Tisseel^{R}, used in the adult population, that have also been approved by global regulatory agencies as an adjunct hemostatic agent in the pediatric population. Both of these fibrin sealants were studied in very small pediatric populations (<30 subjects) which simultaneously enrolled all subjects across age groups as they presented to clinical research centers. The efficacy and safety profile was similar to data observed in the adult population. There was also no observation of enhanced immunogenic responses in the pediatric populations supporting the summary basis for approval. As Fibrocaps is in the same biological class (fibrin sealant with a comparable mechanism of action and biological activity) as Recothrom^{R} and Tisseel^{R}, it is expected that Fibrocaps will not only be found to be a more convenient formulation, but just as safe, effective, and non-immunogenic, as Fibrocaps treatment in the adult population, and Recothrom^{R} & Tisseel^{R} in the pediatric population.

2. Simultaneous enrollment across all four age groups is allowed. This was changed from enrollment utilizing a step-wise sequential approach by age cohort. (sections: protocol synopsis, 3.1)

   Methodology:

   ~~Recruitment will occur in a step-wise, sequential approach with subjects from the 2 oldest age cohorts enrolled first.~~ *Subjects will be enrolled, simultaneously, across four different age groups as they present to clinical sites: 1) 11 years of age to less than 18 years of age; 2) 2 years of age to less than 11 years of age; 3) 6 months of age to less than 2 years of age; or 4) 36 weeks gestational* age *to less than 6 months of age.*

3. The IDMC is afforded more flexibility in approving continued enrollment in a given age cohort. (sections: protocol synopsis, 1.1, 3.1, 10.5.1)

   Methodology:

   Following completion of Visit 5, Day 30, for 6 subjects treated with Fibrocaps plus gelatin sponge *within one of the four age cohort groups, the Independent Data Monitoring Committee will review all available safety data and verify that the observed safety profile supports continued subject enrollment within that given age cohort which has enrolled* 6 Fibrocaps treated subjects. *During this IDMC review, the IDMC will have the authority to approve continued enrollment within a cohort which has enrolled less*

than 6 Fibrocaps treated subjects, if the safety assessment warrants this with a favorable benefit to risk outcome for the subjects.

10.5.1. Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) comprising external experts in pediatric surgery, hematology, and statistics will be charged with monitoring the trial for safety. ~~Two IDMC meetings are planned: the first after 6 subjects aged 11 to less than 18 years have been treated with Fibrocaps and followed for 30 days for safety. The second IDMC meeting will occur after 6 subjects aged 2 to less than 11 years have been treated with Fibrocaps and followed for 30 days for safety~~*. IDMC meetings will occur after 6 subjects have been treated with Fibrocaps and followed for 30 days for safety in any of the 4 age cohorts (i.e., once 6 subjects are enrolled in 1 of the 4 age cohorts, the IDMC will convene once that data set is ready for review). The IDMC will review all available safety data and verify that the observed safety profile supports continued subject enrollment within that given age cohort which has enrolled 6 Fibrocaps treated subjects. During this IDMC review, the IDMC will have the authority to approve continued enrollment within a cohort which has enrolled less than 6 Fibrocaps treated subjects, if the safety assessment warrants this with a favorable benefit to risk outcome for the subjects.*

4. A minimum number of subjects per age cohort are no longer required.(section: protocol synopsis)

Number of Subjects:

The study will enroll a total of approximately 108 subjects. ~~with at least 6 subjects from each age cohort. Approximately 36 subjects will be enrolled in each surgical indication.~~

5. Soft Tissue Surgeries related to burn donor skin grafts are further clarified. (sections: protocol synopsis, 4.0)

Soft tissue Surgery

The TBS will be identified during the soft tissue dissection related to the primary operative procedure. Primary operative procedures include but are not limited to: lower anterior resections, abdominal perineal resections, donor skin graft site *(split-thickness-meshed, split-thickness-non-meshed, full thickness, and composite graft)* in limited burn patients, breast mass excision, cleft lip repair, and hernia repair.

6. Renal and Spinal Surgery indications added. (sections: protocol synopsis, 4.0)

3. Renal Surgery *– Nephrectomy associated with diffuse oozing from the retroperitoneal wall*

4. Spinal Surgery *– Laminectomy, spinal fusion, or other appropriate pediatric spinal surgeries associated with mild to moderate bleeding requiring an adjunct fibrin sealant*

7. Inclusion Criteria clarifications added regarding acceptable gestational age for the newborn cohort. (sections: protocol synopsis, 4.2)

   Inclusion Criteria

   Subjects may be included in the study if they meet all of the following criteria:

   1. Subject age is *36 weeks gestational age* ~~0 days~~ through < 18 years of age at time of randomization

8. Exclusion Criteria regarding acceptable baseline laboratory values clarified. (sections: protocol synopsis, 4.3)

   Exclusion Criteria

   Subjects will be excluded from the study if any of the following exclusion criteria apply prior to randomization:

   1. Baseline abnormalities of international normalized ration (INR) > 2.5 or activated partial thromboplastin time (aPTT) > 100 seconds during screening that are not explained by current drug treatment (e.g., warfarin, heparin), or *chronic disease state necessitating surgery (e.g., end-stage liver disease)*
   2. Platelets < 100 x109 PLT/L during screening, *unless due to chronic disease state, e.g. liver disease/failure, necessitating surgery*
   3. ~~Subject has history of heparin-induced thrombocytopenia (only for vascular subjects where heparin use is required)~~

9. Added current version of Gelfoam Package Insert dated June, 2013(section: Appendix A)

10. Updated Drug Safety Officer Name and Contact Information (section: Title Page)

    Drug Safety Officer: [redacted]
    Drug Safety Physician : [redacted], *MD* [redacted]

11. Added New Section 8.4 Events of Special Interest (section: 8.4)

    8.4. ADVERSE EVENTS OF SPECIAL INTEREST

    During Fibrocaps development, specific categories of AEs were designated as Adverse Events of Special Interest (AESI). These are events that are biologically plausibly associated with Fibrocaps exposure, have been historically associated with the class of topical hemostatic agents, or have been historically associated with drug application using air- or gas-pressurized sprayers. The categories of AESI are:

    - *Surgical site-related events, which includes pain and infection suggestive of a higher complication rate*

- *Thromboembolic events, which includes acute ischemic events like myocardial infarction, deep vein thrombosis and stroke*
- *Re-bleeding at the TBS, including post-procedural hemorrhage and hematomas*
- *Air emboli-associated events, which includes acute respiratory failure or cardiovascular collapse occurring intra-operatively following the use of the Fibrospray device*
- *Hepatitis/HIV infection suggestive of viral transmission through Fibrocaps or Tachosil*

The incidence of these AESI will be monitored according to the standard safety operating procedure for AEs and will be compared to Gelfoam. In addition, additional information will be collected for events of potential air/gas emboli using the Raplixa (Fibrocaps) Air or Gas Embolism Adverse Events questionnaire.

12. Section 8.1.4 Additional Reporting Requirements, new text added.

Medication error: *Refers to any unintended error in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional, patient or consumer. Medication errors are an important cause of morbidity and mortality and many could be prevented or mitigated. They can fall broadly into 4 categories:*

1. Wrong medication

2. Wrong dose (including strength, form, timing, concentration, infusion rate and amount)

3. Wrong route of administration

4. Wrong patient

Occurrences of medication errors in a study subject should be reported within 24 hours using the Medication Error/Overdose form. In cases where a medication error results in a serious adverse event, the Serious Adverse Event reporting form should be used to report the SAE. Non-serious AEs associated with medication errors should be reported in AE page in eCRF.

13. Section 8.1.3 added.

8.1.3. Incident (Article 10 of the MDD in the European Union)

An incident is any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject, or user or of other persons or to a serious deterioration in their state of health.

PROTOCOL ADMINISTRATIVE LETTER DATED 23 JULY 2014

SUMMARY OF CHANGES

THE MEDICINES COMPANY®

RaPid
Raplixa Pediatric Surgery

PROTOCOL ADMINISTRATIVE LETTER

A Phase 2, Randomized, Single-Blind, Controlled Trial of Topical Fibrocaps™ (Raplixa™) in Intraoperative Surgical Hemostasis in a Pediatric Population

TO: All Investigators

FROM: [redacted] MD [redacted] The Medicines Company

DATE: 23 July 2014

RE: Updated FC-007 Protocol Appendix A, Gelfoam Package Insert

Protocol No.: FC-007
U.S. IND No.: 014385
EudraCT No.: 2014-000947-33
PROTOCOL VERSION: Version 2.0, 13 March 2014

Dear Investigator:

The purpose of this administrative letter is to provide you with an updated Gelfoam absorbable gelatin sponge package insert. The protocol, Appendix A currently contains an outdated version of the Gelfoam package insert dated August, 2003. Attached is an updated Gelfoam package insert dated June, 2013 for your reference.

This update is considered an administrative protocol change and as it does not have an effect on the study procedures, clinical assessments or subject safety. Please maintain a copy of this administrative letter with your protocol and provide a copy to your Institutional Review Board/ Ethics Committee.

Please sign below and return a copy of this memo to PPD.

I acknowledge receipt of this Administrative Change to the FC-007 protocol.

Investigator Signature _____ Date _____

Investigator Printed Name _____ Institution _____

PROTOCOL AMENDMENT 2 DATED 13 MARCH 2014

SUMMARY OF CHANGES

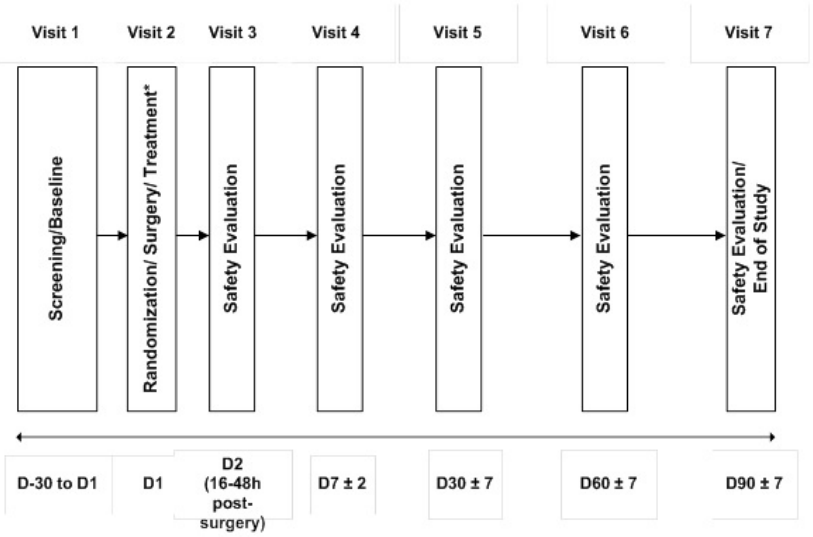
The following significant changes were made to protocol FC-007 version 1.0. All changes are reflected in version 2.0 of the protocol dated 13-Mar-2014.
The EudraCT number has been confirmed and updated. Minor administrative changes were made for consistency and are not all listed here. No additional assessments or changes in risk to the subject have been made. Additional monitoring for anti-fibrinogen antibodies, for subjects found positive for anti-thrombin antibodies, is a request from the FDA.
Items in *italics* were added, while strikethrough text (i.e., ~~text~~) has been deleted.

1. **Study Population (Section 1.4) – Clarified to be consistent with EMA agreement for the Pediatric Investigational Plan**

   ~~The pediatric population will be treated in this study. The ages will be segregated into 4 groups according to European Medicines Agency (EMA) requirements (EMEA, CPMP/ICH/2711/99; FDA, ICH E11, December 2000):~~
   ~~• Term newborn infants (0–27 days)~~
   ~~• Infants and toddlers (28 days–23 months)~~
   ~~• Children (2–11 years)~~
   ~~• Adolescents (12–17 years)~~

   The ages will be segregated into 4 groups which are generally consistent with the European Medicines Agency (EMA) (EMEA, CPMP/ICH/2711/99) and the FDA, (ICH E11, December 2000) requirements:
   - *Birth to less than 6 months*
   - *6 months to less than 2 years*
   - *Children (2 years to less than 11 years)*
   - *Adolescents (11 to less than 18 years)*

2. ***Schematic Diagram of Trial Design (Section 3.2, Figure 1) –Included to provide overall study schema.***



3. Inclusion Criteria (Synopsis, Section 4.2) – Clarified to include sexually active teenagers.

a. If a subject is ≥ 7 years old, or appropriate age as defined by local regulations, the subject ~~is~~ *may be* required to have signed an IRB-approved assent document

b. *If subject is a sexually active male or a sexually active female of child-bearing potential, subject agrees to use a medically accepted form of contraception from the time of consent to completion of all of the follow-up study visits.*

4. Laboratory Assessments (Section 7.1.5) and Safety Analysis (Section 10.4.4) – included request by the FDA to assess anti-fibrinogen antibodies in subjects with a positive anti-thrombin

a. Section 7.1.5 Laboratory Assessments

Immunogenicity Sample

This blood sample will be used for measuring anti-thrombin *and anti-fibrinogen* antibodies in plasma from all subjects treated in the study.

b. Section 10.4.4 Safety Analysis

Overall safety, as determined by the incidence, severity and relationship of adverse events (AEs), clinical laboratory abnormalities, estimated rates of immunogenicity *(monitoring for anti-thrombin antibodies and additional*

monitoring for anti-fibrinogen antibodies will be limited to subjects found positive for anti-thrombin antibodies and subjects with unexplained bleeding or clinical suspicion of bleeding related to antibody formation) and post-surgery bleeding complications.

5. AE Severity (Section 8.1.1.1) – provided clarification of severity grading consistent with CTCAE criteria.

~~The severity of an AE and the relationship to study drug will be assessed by the investigator. The investigator should ensure that any subject experiencing an AE receives appropriate medical support until the event resolves.~~

~~Adverse events (AE) will be graded on a 3-point scale and reported as indicated on the case report form. The intensity of an AE is defined as follows:~~

~~1 = Mild: Discomfort noticed, but no disruption to daily activity.~~

~~2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.~~

~~3 = Severe: Inability to work or perform normal daily activity.~~

AE severity will be assessed according to the grading scale in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0:

a. ***Grade 1****: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.*

b. ***Grade 2****: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*.*

c. ***Grade 3****: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.*

d. ***Grade*** *4: Life-threatening consequences; urgent intervention indicated.*

e. ***Grade 5****: Death related to AE.*

**Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

***Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden*

6. Bleeding Events (Section 10.4.4.1) – Section deleted, as the methodology is not pertinent to endpoints nor the pediatric population

~~The incidence of hemorrhage will be measured by clinically relevant criteria (Global Utilization of Streptokinase and Tpa for Occluded Arteries [GUSTO], Thrombolysis in Myocardial Infarction [TIMI], and other major bleeding scales) for up to 48 hours. Data will be summarized for the following:~~

- ~~Incidence of hemorrhage by clinically relevant criteria/scales up through 48 hours~~
- ~~Incidence of blood product transfusion(s) up through 48 hours, categorized according to relationship with coronary artery bypass grafting (CABG) surgery~~

EMERGENCY CONTACTS

Emergency Contact Information

Role in Study	Name	Contact Information
Primary Contact:		
Medical Monitor	[redacted], MD Mallinckrodt Pharmaceuticals 675 McDonnell Boulevard Hazelwood, MO 63042 United States of America	Telephone: [redacted] Cell phone: [redacted] E-mail: (not for emergencies): [redacted]

Please see next page for additional telephone contact numbers (Page 16).

Please see Section 8.3 for detailed information regarding the Serious Adverse Event (SAE) Reporting Requirements for both the biologics and the devices of this study.

SAE reporting fax: [redacted]

SAE confirmation phone: [redacted] (24-hour call center)

SAE confirmation email: GlobalPV@mallinckrodt.com

Additional Contacts

Role in Study	Name	Contact Information
Clinical Trial Manager	[redacted] Mallinckrodt Pharmaceuticals	Cell: [redacted] E-mail: [redacted]
Clinical Technical Lead	[redacted], PharmD, MBA, RPh, BCPS Mallinckrodt Pharmaceuticals [redacted]	Telephone: [redacted] Cell: [redacted] E-mail: [redacted]
Biostatistics	[redacted] Mallinckrodt Pharmaceuticals [redacted]	Telephone: [redacted] E-mail: [redacted]
Safety Physician (For the drug and for the devices)	[redacted], MD, PhD Mallinckrodt Pharmaceuticals	Telephone: [redacted] Cell: [redacted] E-mail (not for emergencies): [redacted]

The Clinical Technical Lead is authorized to sign this protocol for the sponsor.

SIGNATURE PAGE

SPONSOR SIGNATURE

My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and applicable laws and other regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the US Code of Federal Regulations (CFR), protections for privacy, and generally accepted ethical principles for human research such as the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care.

Sponsor Signature	Date of Signature (DD Month YYYY)
Sponsor Name (print)	

SIGNATURE PAGE

INVESTIGATOR SIGNATURE

My signature confirms that the clinical study will be conducted in accordance with the protocol and applicable laws and other regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the US Code of Federal Regulations (CFR), protections for privacy, and generally accepted ethical principles such as the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care.

Investigator's Signature	Date of Signature (DD Month YYYY)

Investigator's Name and Title (print)

LIST OF ABBREVIATIONS

AE	adverse event
AESI	Adverse event of special interest
ALAT/ALT	alanine aminotransferase
Alb	albumin
aPTT	activated partial thromboplastin time
ASAT/AST	aspartate aminotransferase
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
Cr	creatinine
CRF	case report form
DCF	Data clarification forms
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOS	end of study visit
EU	European Union
FDA	Food and Drug Administration
FFP	Fresh frozen plasma
G	gelatin sponge (control group)
GCP	Good Clinical Practice
GPV	Global Pharmacovigilance Department
Glu	glucose
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
IU	international units
K	potassium
L	liter
MDR	Medical Device Reporting

MDV	Medical Device Vigilance
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MH	medical history
MI	myocardial infarction
NA	sodium
OBS	other bleeding sites
PE	physical examination
PI	Principal Investigator
PLT	platelets
PRBC	Packed red blood cell
psi	pounds per square inch
PT	prothrombin time
PTFE	polytetrafluoroethylene
SAE	serious adverse event
SAP	statistical analysis plan
Screen failure	subject does not meet all inclusion criteria/exclusion criteria
SD	standard deviation
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TBili	total bilirubin
TBS	target bleeding site
Treated	treated with Study Treatment (R+G or G)
TTH	time to hemostasis
USA/US	United States of America
USP	United States Pharmacopeia
USPI	United States Pharmacopoeia
WHODD	WHO Drug Dictionary

PROTOCOL SYNOPSIS

Name of Sponsor/Company: Mallinckrodt Pharmaceuticals
Name of Finished Product: Raplixa™ [Fibrocaps™ (PRO-0601)]
Name of Active Ingredient: Human Plasma-derived Thrombin and Fibrinogen
Title of Study: A Phase 2, Randomized, Single-Blind, Controlled Trial of Raplixa in Intraoperative Surgical Hemostasis in a Pediatric Population
Phase of Development: 2
Study Centers: Up to 25 centers in the United States (US)
Study Period: The estimated study period is approximately 30 months from first subject enrolled to last subject completed. Estimated date first subject enrolled: December 2014 Estimated date last subject completed: July 2018
Objectives: The objective of the study is to evaluate the efficacy and safety of Raplixa plus gelatin sponge, as compared to gelatin sponge alone, for achieving hemostasis in pediatric subjects undergoing hepatic, renal, soft tissue, spinal, or vascular surgery.
Methodology: The study is a Phase 2, multicenter, randomized, single-blind (to subjects), controlled trial comparing the efficacy and safety of Raplixa in combination with an absorbable gelatin sponge to gelatin sponge alone. The study will enroll subjects undergoing one of the following surgical procedures: hepatic, renal, soft tissue, spinal, or vascular surgery. Parents/guardians of subjects will provide written informed consent prior to undergoing any protocol-related assessments or procedures, which may occur up to 30 days prior to surgery. Subjects ≥ 7 years old, or of appropriate age as defined by local regulations, may be required to provide assent to participate in the study. After establishing eligibility during screening and confirming continued eligibility on the day of surgery (Day 1), subjects will be randomized in a single-blinded manner, in a 2:1 ratio, to receive study drug (either Raplixa in combination with an absorbable gelatin sponge [active group; R+G] or gelatin sponge alone [control group; G]) when an appropriate target bleeding site (TBS) is identified. Subjects who are not treated will be withdrawn from the study and may be replaced. Reasons for not receiving study drug include, but are not limited to; lack of an appropriate TBS for time to hemostasis (TTH) evaluation, severe bleeding, or a change in surgical procedure that renders the subject ineligible, after the subject has been randomized. Subjects will be enrolled across 4 different age groups, with the 2 oldest age groups being enrolled simultaneously: • Adolescents (11 to less than 18 years). • Children (2 years to less than 11 years). • 6 months to less than 2 years. • Birth (≥ 36 weeks gestational age at birth) to less than 6 months. During a surgical procedure on Day 1 (Visit 2), subjects will be initially treated with Raplixa plus gelatin sponge or gelatin sponge alone at the TBS. The TTH will be assessed every 30 seconds for up to 5 minutes. Bleeding appropriate for TTH evaluation is defined as mild to moderate bleeding, either on its own or remaining after brisk/severe bleeding has been controlled by standard surgical modalities. Subjects may be re-treated with their assigned treatment as necessary during the 5-minute TTH assessment period, with up to a maximum of 2 vials of Raplixa (2.0 g) in total (for

target and non-target bleeding sites). Rescue treatment may be administered if necessary in a tiered approach at the TBS or other bleeding sites (OBS) with thrombin-containing hemostats permitted after all other treatment options have been attempted after the TTH assessment period has elapsed, at the discretion of the Investigator.

For subjects randomized to Raplixa, at any time after hemostasis has been achieved at the TBS, and the 5-minute TTH assessment period has elapsed, the remaining Raplixa may be used at additional appropriate OBS that are part of the primary surgical procedure. Importantly, the remaining Raplixa should not be used on OBS until after the 5-minute TTH assessment period has elapsed in order to ensure that adequate Raplixa is available to use in the event of re-bleeding from the TBS. The amount of Raplixa applied and the incidence of hemostasis achieved at OBS will be recorded; however, the primary efficacy analysis will not include hemostasis data from the OBS.

Subjects will undergo a safety evaluation consisting of a targeted physical examination and clinical laboratory tests on Day 2 (Visit 3). If the subject's surgery was performed as an outpatient procedure, the Visit 3 assessment may be conducted over the phone with the physical examination conducted and laboratory tests collected prior to discharge on Day 1. Safety evaluations will also be performed on Day 7 (Visit 4) via telephone, if the subject has been discharged, and on Day 30 (Visit 5; End of Study Visit). Immunogenicity samples (monitoring for anti-thrombin antibodies) will be collected and analyzed at baseline and at Day 30 for all treated subjects, except subjects who are less than 6 months old. Additional monitoring for anti-fibrinogen antibodies will be limited to subjects found positive for anti-thrombin antibodies and subjects with unexplained bleeding or clinical suspicion of bleeding related to antibody formation.

Number of Subjects:

The study will enroll a total of up to 87 subjects.

Diagnosis and Main Criteria for Selection:

The study will enroll subjects undergoing one of the following surgical procedures:

1. Hepatic Surgery

Hepatic wedge resection or anatomic resection of 1 to 5 contiguous hepatic segments, which may be combined with surgical procedures involving the pancreas, gall bladder, bile duct or intestines. Subjects undergoing living-related liver donation are also eligible.

2. Renal Surgery

Nephrectomy associated with diffuse oozing from the retroperitoneal wall.

3. Soft Tissue Surgery

The TBS will be identified during the soft tissue dissection related to the primary operative procedure. Primary operative procedures include but are not limited to: lower anterior resections, abdominal perineal resections, donor skin graft site (split-thickness-meshed, split-thickness-non-meshed, full thickness and composite graft) in limited burn patients (up to 40% total body surface area [TBSA]), breast mass excision, cleft lip repair, and hernia repair.

Appropriate soft tissue types will include but will not be limited to: loose areolar tissue, fat, lymphatic tissue/lymph node beds, and muscle. The TBS will not involve parenchymal, gastrointestinal or genitourinary soft tissue, and cardiac, lung or brain tissue, as Raplixa has not yet been studied in these tissue types.

4. Spinal Surgery

Scoliosis surgery, cervical, thoracic, or lumbar discectomy, corpectomy, laminectomy, lateral or interbody fusion. Epidural bleeding typically described as oozing, flowing, or pulsatile, and normally requiring topical adjuncts to hemostasis is necessary to be considered eligible. The TBS may not be within a bony cavity or other confined area.

5. Vascular Surgery

All subjects undergoing vascular surgery should be systemically heparinized according to standard procedures. The clamp(s) should be removed to determine if an appropriate TBS with

mild to moderate bleeding is present. The clamp(s) should remain off once a TBS is identified and during the treatment and assessment of TTH. If protamine reversal is indicated, it should occur after the 5-minute TTH assessment period is completed, unless a safety concern dictates that it should happen earlier. Appropriate vascular surgical procedures may include, but are not limited to: artificial graft (i.e., polytetrafluoroethylene [PTFE] or Dacron) for hemodialysis access (including revision procedures), hemangiomas, and vascular injuries (peripheral or abdominal). The TBS may not involve the heart or the vessels surrounding the heart.

Inclusion Criteria

Subjects may be included in the study if they meet all of the following criteria:

1. Subject age is ≥ 36 weeks gestational age at birth (for infants) through < 18 years of age at time of treatment.
2. Subject's legal representative (parent or guardian) has signed an institutional review board (IRB)-approved informed consent document.
3. If a subject is ≥ 7 years old, or appropriate age as defined by local regulations, the subject may be required to have signed an IRB-approved assent document.
4. Subject is scheduled to undergo one of the surgical procedures described in the protocol.
5. If female and of child-bearing potential, subject has a negative pregnancy test on the day of surgery
6. If subject is a sexually active male or a sexually active female of child-bearing potential, subject agrees to use a medically accepted form of contraception from the time of consent to completion of all of the follow-up study visits.

During Surgery Inclusion Criteria

1. Presence of mild or moderate bleeding/oozing.
2. TBS surface area of ≤ 100 cm^2.
3. Subject has not received any whole blood, fresh frozen plasma (FFP), cryoprecipitate, or platelets within 24 hours prior to study drug. Packed red blood cell (PRBC) transfusions are allowed.
4. Subject has no intra-operative complication other than bleeding which, in the opinion of the Investigator, may interfere with the assessment of efficacy or safety.

Exclusion Criteria

Subjects will be excluded from the study if any of the following exclusion criteria apply prior to enrollment:

1. Gestational age of < 36 weeks at birth (for infants less than 6 months).
2. Subject has any clinically-significant congenital coagulation disorder (e.g., hemophilia A or B) that may interfere with the assessment of efficacy or pose a safety risk to the subject according to the Investigator.
3. Subject has baseline abnormalities of international normalized ratio (INR) > 2.5 or activated partial thromboplastin time (aPTT) > 100 seconds during screening that are not explained by current drug treatment (e.g., warfarin, heparin), or chronic disease state necessitating surgery (e.g., end-stage liver disease).

4. Subject has aspartate aminotransferase (ASAT/AST) and alanine aminotransferase (ALAT/ALT) > 3 times the upper limit of reference range during screening, except for subjects undergoing liver resection surgery or with a diagnosis of liver disease where there is no upper limit for these analytes due to the nature of their disease.
5. Subject is unwilling to receive blood products or products derived from human blood.
6. Subject has platelets < 100 $x10^9$ PLT/L during screening, unless due to chronic disease state, e.g., liver disease/failure, necessitating surgery.
7. Subject has known antibodies or hypersensitivity to Raplixa or any of its components, other thrombin preparations, or coagulation factors.
8. Subject has known allergy to porcine gelatin.
9. Subject has medical, social, or psychosocial factors that, in the opinion of the Investigator, could impact subject safety or compliance with study procedures.
10. Subject is; 1) currently participating in another clinical study or 2) has participated in another clinical study within 30 days of Screening or 3) plans to participate in a clinical study prior to completion of the 30-day follow-up period.

Test Product, Dose and Mode of Administration, Batch Number(s):

Raplixa contains a spray-dried mixture of human plasma-derived fibrinogen and human plasma-derived thrombin powders that was developed under the general guidelines that support marketing of fibrin sealant products manufactured for commercial use.

Raplixa is used without reconstitution and can be applied onto the surgical bleeding site directly from the vial or with the use of the RaplixaSpray device, or onto a moistened gelatin sponge that is then applied to the surgical bleeding site. Raplixa dissolves readily on contact with aqueous fluids (e.g., blood) activating thrombin which triggers an immediate conversion of fibrinogen into fibrin, and subsequent clot formation.

The physicochemical properties of Raplixa make it a unique fibrin sealant that is ready-to-use, room-temperature stable and convenient to apply to bleeding sites of various sizes and shapes, thus eliminating costly storage, transport, and preparation that is necessary with other currently commercially-available fibrin sealants in the US/European Union (EU).

Duration of Treatment:

Each subject will be treated during a single surgical procedure and will participate in the study for up to 30 days post-surgery.

Reference Therapy, Dose and Mode of Administration:

The control arm consists of a gelatin sponge, supplied by the sponsor, and is the same as is used with Raplixa. Sites will use Gelfoam® (Absorbable Gelatin Sponge, USP, Pfizer). Sites may use their own operating room supply of absorbable gelatin sponge (Gelfoam), if necessary, and must record the name, lot number, and expiration date. The gelatin sponge is cut to the appropriate size and applied topically, dry or moistened, according to the manufacturer's package insert, followed by manual pressure with sterile gauze. If possible, the gelatin sponge should be left in place, while the excess is removed from the bleeding site once hemostasis has been achieved.

Criteria for Evaluation:

Safety:

Overall safety, as determined by the incidence, severity and relationship of adverse events (AEs), clinical laboratory abnormalities, estimated rates of immunogenicity (monitoring for anti-thrombin antibodies) collected and analyzed at baseline and at Day 30 for all treated subjects, except subjects who are less than 6 months old. Additional monitoring for anti-fibrinogen antibodies will be limited to subjects found positive for anti-thrombin antibodies and subjects with unexplained bleeding or clinical suspicion of bleeding related to antibody formation and post-surgery bleeding complications.

Study participation ends after the Day 30 visit. However, should a subject return to the investigator between Day 30 and Day 90 for routine follow-up visits (not scheduled for the purpose of the study), the investigator will record any update in the subject's safety information and report such information to the Sponsor using the data collection forms provided.

Efficacy:

- Percentage/proportion of subjects who reach hemostasis from the first identified TBS within 4 minutes of study drug application.
- Restricted mean TTH (during the 5-minute TTH assessment period).
- Through to Visit 5 (End of Study [EOS]) visit:
    - Use of alternative hemostatic agents on the TBS.
    - Volume of transfused blood (whole blood, fresh frozen plasma (FFP), cryoprecipitate, platelets, or packed red blood cell (PRBC).
    - Incidence of re-operation for bleeding at the TBS.

Statistical Methods:

This is a Phase 2, multicenter, randomized, single blind (for subjects), controlled study to evaluate the safety and efficacy of Raplixa (R) in combination with an absorbable gelatin sponge (R+G) to gelatin sponge alone (G) for achieving hemostasis in pediatric subjects undergoing hepatic, renal, soft tissue, spinal or vascular surgery. Randomization is in a 2:1 ratio between R+G and G groups.

The sample size estimation is based on data from the completed Phase 3 trial (FC-004). Assuming the proportion of subjects achieving hemostasis within 4 minutes in R+G and G are 87% and 60% respectively, approximately 87 pediatric subjects (58 in R+G, 29 in G) will provide approximately 80% power to detect this difference at the one-sided significance level of 0.025 (equivalently, 2-sided significance level of 0.05) based on a chi-square test for 2 proportions.

Statistical analyses will be performed using the following subject populations:

Intent-to-Treat (ITT) population: The ITT population consists of all randomized subjects. This population will be the primary population for the efficacy analyses.

Safety population: All subjects who received any amount of study drug. This population will be the primary population for the safety analyses.

Descriptive statistics and graphical displays will be used to summarize data collected in the electronic case report forms (eCRF). Continuous variables will be summarized using mean, standard deviation, median, inter-quartile range, minimum and maximum. Categorical variables will be summarized using frequency and percentage. Time-to-event variables will be summarized using Kaplan-Meier estimates.

All relevant subjects' data, including those subjects who are not treated in the study, will be presented in data listings.

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1. INTRODUCTION

The purpose of this study is to evaluate the use of Raplixa in the pediatric surgical population. This study will be conducted in compliance with Good Clinical Practices (GCP) including the Declaration of Helsinki and all applicable regulatory requirements.

1.1. BACKGROUND

The use of topical hemostats, such as fibrin sealants comprising plasma-derived fibrinogen mixed with biologically active thrombin, has been reported since the mid-1940s (1). Commercially-available fibrin sealants have been licensed in the United States and provide an alternative approach to achieve hemostasis during surgical procedures when bleeding cannot be controlled by standard surgical or mechanical techniques (2-6). Fibrin sealants mimic the last stage of the human coagulation system to support local hemostasis as they generate semi-rigid, cross-linked fibrin clots that bind the surface of injured tissues to seal surfaces, support sutures, and/or improve repair or healing of the tissues. The mechanism of action of Raplixa, like that of other fibrin sealants, is based on thrombin's enzymatic activity that catalyzes the conversion of fibrinogen into fibrin monomers that polymerize spontaneously to form a fibrin clot. The thrombin in Raplixa also activates endogenous factor XIII which crosslinks fibrin to create a firm and dissolution-resistant clot that promotes local and rapid hemostasis at the site of application. Because Raplixa dissolves in blood at the bleeding site, blood cells, platelets, and circulating plasma proteins are incorporated into the clot that resembles the natural fibrin clot that is formed during endogenous blood coagulation. As with other fibrin sealants, Raplixa is degraded and metabolized similar to the process by which intrinsic degradation of natural clots of fibrinogen and thrombin occurs.

Raplixa and the RaplixaSpray device are approved for use in adults by the European Union (March 2015) and by the FDA (April 2015):

> http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002807/human_med_001854.jsp&mid=WC0b01ac058001d124
>
> http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM445346.pdf

Raplixa is indicated as an adjunct to hemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. Raplixa is used in conjunction with an absorbable gelatin sponge (USP) and is applied directly or using the RaplixaSpray device (7).

Although there are physiologic differences in the levels of coagulation & fibrinolytic proteins over the maturation of children compared to adults, near adult levels are achieved by most children by 6 months of age, and these differences are considered to be physiologic, i.e., something that is normal, not due to anything pathologic nor significant in terms of causing illness (8, 9).

In current practice, typical fibrin sealants consist of human plasma-derived thrombin and fibrinogen that are filled and stored separately to avoid thrombin's enzymatic activity on fibrinogen before application to the intended site of action. In addition, most commercially-available products are stored frozen and must be thawed or reconstituted before they can be applied to a wound site. To improve the convenience and flexibility of use, Raplixa has been designed as a room temperature stable, ready-to-use powder fibrin sealant that dissolves and activates on contact when sprayed onto a bleeding or oozing wound site.

To date, there are 3 topical hemostats, Recothrom® and Tisseel® used in the adult population, that have also been approved by regulatory agencies as adjuncts to hemostasis in the pediatric population. These products were studied in very small pediatric populations (≤ 30 subjects) which simultaneously enrolled all subjects across age groups as they presented to clinical research centers. The efficacy and safety profile was similar to data observed in the adult population. There was no observation of enhanced immunogenic responses in the pediatric populations supporting the summary basis for approval. As Raplixa is a pharmacologically active topical hemostat approved for use in pediatric patients as are Recothrom® and Tisseell®, it is expected that Raplixa will have a similar safety, efficacy, and non-immunogenic profile in pediatric patients as Raplixa treatment in the adult population.

1.1.1. Preclinical Studies

Raplixa was shown to be effective in multiple animal models of mild and moderate surgical bleeding. The use of Raplixa was effective alone, but appeared to be enhanced in certain models when used in combination with a pressure sheet. Raplixa was locally and systemically non-toxic, and did not promote intra-abdominal adhesion formation when applied to non-target organs. In addition, the RaplixaSpray device was shown to have a low risk of producing air emboli when used correctly and incorrectly during hepatic resection surgery. The nonclinical efficacy and safety data generated support the clinical development of Raplixa and the RaplixaSpray device to promote hemostasis in surgical bleeding. For additional information please refer to the Investigator's Brochure (IB) and the Raplixa package insert.

1.1.2. Clinical Studies

Two Phase 2 trials (Verhoef, et al) (10) and one Phase 3 trial (Bochicchio, et al) (11) have been performed in different surgical indications to evaluate the efficacy and safety of Raplixa. The trials were performed in accordance with the clinical trial designs recommended by the CHMP for fibrin sealants (Guideline on the Clinical Investigation of Plasma Derived Fibrin Sealant/Haemostatic products; CPMP/BPWG/1089/00) and the FDA (Guidance for Industry: Efficacy Studies to Support Marketing of Fibrin Sealant Products Manufactured for Commercial Use, May 1999).

The clinical safety and efficacy of Raplixa were initially evaluated in 2 Phase 2 studies (FC-002 US and FC-002 NL) in surgical indications where adjuncts to hemostasis are required to control bleeding: spinal surgery, major hepatic resection, and peripheral vascular surgery (i.e., peripheral arterial bypass surgery and arteriovenous graft formation for hemodialysis access). Each of these types of surgery is characterized by diffuse and difficult to control, mild to moderate bleeding, frequently requiring the use of adjuncts to hemostasis.

In FC-002 NL, 56 subjects undergoing hepatic resection surgery were randomized 2:1 to receive Raplixa plus gelatin sponge (n=39) or gelatin sponge alone (n=17). In the Intent-to-Treat (ITT) analysis, a statistically significant reduction in the meantime to hemostasis (TTH) was observed with Raplixa, as compared to gelatin sponge alone (2.2 minutes vs 4.4 minutes, p=0.004). In FC-002 US, 70 subjects undergoing spinal, vascular, or general surgery were randomized 2:1 to Raplixa plus gelatin sponge (n=47) or gelatin sponge alone (n=23). A statistically significant reduction in the mean TTH was also observed with Raplixa in the ITT analysis, as compared to gelatin sponge alone (1.9 minutes vs 4.8 minutes, p<0.001).

The safety profile of Raplixa plus gelatin sponge across both FC-002 studies (n=86) was considered acceptable. The most common (>10% of subjects) treatment-emergent adverse events (TEAEs) being post-operative pain, constipation, nausea, edema, vomiting and hypokalemia. The majority of TEAEs were classified as mild or moderate in intensity. Thirty-five treatment-emergent serious AEs (TESAEs) were reported, with 25 reported from subjects undergoing liver resection surgery and only one considered possibly related to Raplixa by the Investigator. There were no observed Raplixa-associated trends or safety signals related to changes in vital signs, physical examinations, coagulation laboratory parameters or anti-thrombin neutralizing antibodies.

A total of 721 subjects undergoing hepatic resection, spinal surgery, vascular surgery and soft tissue dissection surgery were randomized in FC-004, a Phase 3, international, multi-center, single-blind, controlled trial (11). All primary and secondary efficacy endpoints in this study were met, with the median TTH for each surgery type being significantly shorter with Raplixa plus gelatin sponge than with gelatin sponge alone (p<0.0001). In all surgical indications, a significantly higher proportion of subjects achieved hemostasis at 3 and 5 minutes after application with Raplixa plus gelatin sponge than with gelatin sponge alone (p<0.0001). Results of the Phase 3 study indicated that Raplixa and the RaplixaSpray device appeared to be safe and well tolerated. The adverse events (AEs) reported in the trial were consistent with those expected in subjects undergoing spinal, vascular, hepatic resection, and soft tissue dissection surgical procedures under general anesthesia and the nature of the subjects' underlying diseases.

1.1.3. Known and Potential Risks and Benefits

This is the first trial of Raplixa in a pediatric population. Raplixa and the RaplixaSpray device are approved for use in adults by the European Union (March 2015) and by the FDA (April 2015):

Contraindications for Raplixa use are as follows.

Do not use:

- Intravascularly.
- For the treatment of severe or brisk arterial bleeding.
- In patients known to have anaphylactic or severe systemic reactions to human blood products.

The Warnings and Precautions for Raplixa/RaplixaSpray device are as follows:

- Thromboembolic events may result from intravascular application of Raplixa.
- Air or gas embolism can occur when using air- or gas-pressurized sprayers to administer fibrin sealants. Operate the device according to the manufacturer's instructions.
- Raplixa may carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agents, despite manufacturing steps designed to reduce the risk of viral transmission.
- Allergic type hypersensitivity reactions may occur. If allergic type hypersensitivity symptoms occur, discontinue administration immediately.

Please consult the United States Pharmacopoeia (USPI) for further information.

1.2. STUDY RATIONALE

This study is being conducted to determine the safety and efficacy of Raplixa for achieving hemostasis in pediatric subjects undergoing hepatic, renal, soft tissue, spinal, or vascular surgery. Raplixa and the RaplixaSpray device are approved for use in adults, but have not previously been evaluated in pediatric subjects. Topical hemostats, Recothrom® and Tisseel®, have previously been evaluated and approved by regulatory agencies for use in pediatric patients. The safety profile of these products in pediatric patients was similar to that in adult patients and there was no observation of enhanced immunogenic responses in the pediatric population. As Raplixa is a pharmacologically active topical hemostat as are Recothrom® and Tisseel ®, it is expected that Raplixa will have a similar safety, efficacy, and non-immunogenic profile in pediatric patients as Raplixa treatment in the adult population.

1.3. STUDY POPULATION

Pediatric subjects will be treated in this study, with the 2 oldest age groups enrolled simultaneously first. Subjects will be segregated into 4 age groups which are generally consistent with the European Medicines Agency (EMA) (EMEA, CPMP/ICH/2711/99) and the FDA (ICH E11, December 2000) requirements:

- Adolescents (11 to less than 18 years).
- Children (2 years to less than 11 years).
- 6 months to less than 2 years.
- Birth (≥ 36 weeks gestational age at birth) to less than 6 months.

2. TRIAL OBJECTIVES AND PURPOSE

The objective of the study is to evaluate the efficacy and safety of Raplixa plus gelatin sponge, as compared to gelatin sponge alone, for achieving hemostasis in pediatric subjects undergoing hepatic, renal, soft tissue, spinal, or vascular surgery.

3. TRIAL DESIGN

3.1. TYPE/DESIGN OF TRIAL

This is a Phase 2, multicenter, randomized, single-blind, controlled trial comparing the efficacy and safety of Raplixa in combination with an absorbable gelatin sponge to gelatin sponge alone, in pediatric subjects undergoing hepatic, renal, soft tissue, spinal, or vascular surgery. The study will enroll approximately 87 subjects at up to 25 sites in the US.

Informed consent will be obtained from parents/guardians for each subject before any protocol-related assessments or procedures are conducted. Subjects 7 years and older, or of an appropriate age as defined by local regulations, may be required to provide assent to participate in the study.

Eligible subjects will be randomized in a 2:1 ratio to receive treatment with Raplixa in combination with an absorbable gelatin sponge (active group; R+G) or gelatin sponge alone (control group; G) when an appropriate target bleeding site (TBS) is identified. Subjects who are not treated with study drug will be withdrawn from the study and may be replaced.

Reasons for not receiving study drug include, but are not limited to; lack of an appropriate TBS for time to hemostasis (TTH) evaluation, severe bleeding, or a change in surgical procedure that renders the subject ineligible, after the subject has been randomized.

Subjects will be enrolled across 4 different age groups, with the 2 oldest age groups enrolled simultaneously: 1) 11 years of age to less than 18 years of age; 2) 2 years of age to less than 11 years of age; 3) 6 months of age to less than 2 years of age; or 4) ≥ 36 weeks gestational age at birth to less than 6 months of age. Following completion of Visit 5, Day 30, for 6 subjects treated with Raplixa plus gelatin sponge within 1 of the 2 oldest age groups, the Independent Data Monitoring Committee (IDMC) will review all available safety data and verify that the observed safety profile supports continued subject enrollment. Study enrollment will not be stopped during the IDMC review. After the IDMC review, this body will notify the study team if the safety assessment shows that there is a favorable benefit-to-risk outcome to continue enrollment in the two older cohorts, and whether it is acceptable to initiate sequential enrollment in the two lower age cohorts.

During a surgical procedure on Day 1 (Visit 2), subjects will be initially treated with up to one vial of Raplixa (1.0 g) plus gelatin sponge or gelatin sponge alone at the TBS. The TTH will be assessed every 30 seconds for up to 5 minutes. Bleeding appropriate for TTH evaluation is defined as mild to moderate bleeding, either on its own or remaining after brisk/severe bleeding has been controlled by standard surgical modalities. Subjects may be retreated with their assigned treatment as necessary during the 5-minute TTH assessment period, with up to a maximum of 2 vials of Raplixa (2.0 g) in total (for target and non-target bleeding sites). Rescue treatment may be administered at the TBS or OBS if necessary in a

tiered approach after the 5-minute TTH assessment period has elapsed, at the discretion of the Investigator (see Section 5.5 for details).

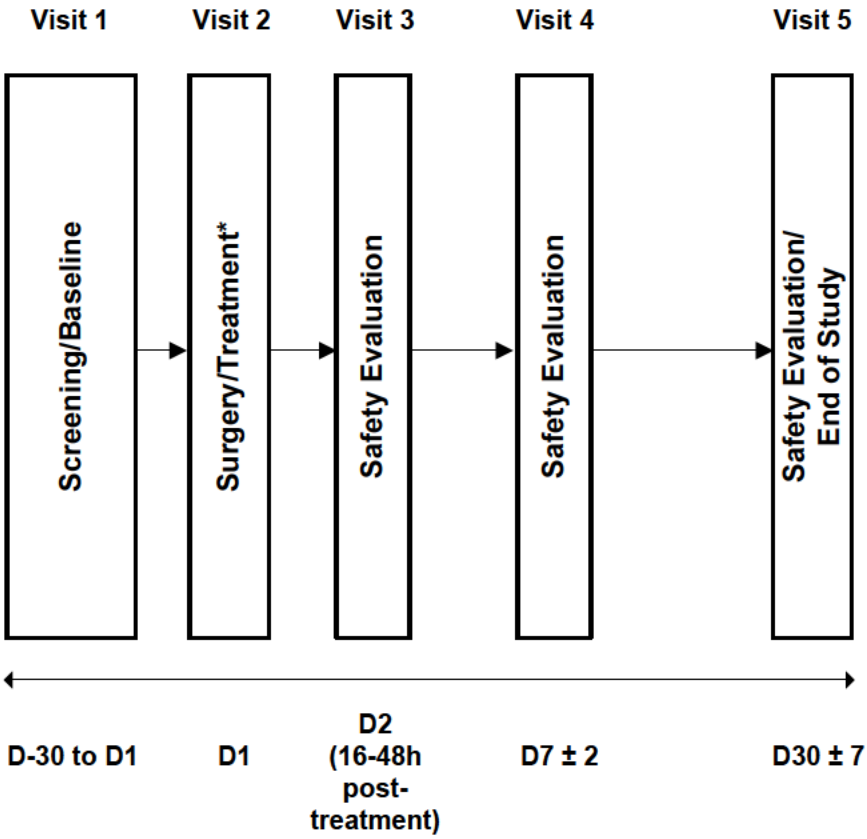
For subjects who are randomized and receive Raplixa, at any time after hemostasis has been achieved at the TBS and the 5-minute TTH assessment period has elapsed, the remaining Raplixa may be used at additional appropriate OBS that are part of the primary surgical procedure. Importantly, the remaining Raplixa should not be used on OBS until after the 5-minute TTH assessment period has elapsed in order to ensure that adequate Raplixa is available to use in the event of re-bleeding from the TBS. The amount of Raplixa applied and the incidence of hemostasis achieved at OBS will be recorded; however, the primary efficacy analysis will not include hemostasis data from the OBS.

Subjects will undergo a safety evaluation consisting of a targeted physical examination and clinical laboratory tests on Day 2 (Visit 3). If the subject's surgery was performed as an outpatient procedure, the Visit 3 assessment may be conducted over the phone with the physical examination conducted and laboratory tests collected prior to discharge on Day 1. Safety evaluations will also be performed on Day 7 (Visit 4), via telephone, if the subject has been discharged, and on Day 30 (Visit 5; End of Study visit). Immunogenicity samples (monitoring for anti-thrombin antibodies) will be collected and analyzed at baseline and at Day 30 for all treated subjects, except subjects who are less than 6 months old. Additional monitoring for anti-fibrinogen antibodies will be limited to subjects found positive for anti-thrombin antibodies and subjects with unexplained bleeding or clinical suspicion of bleeding related to antibody formation.

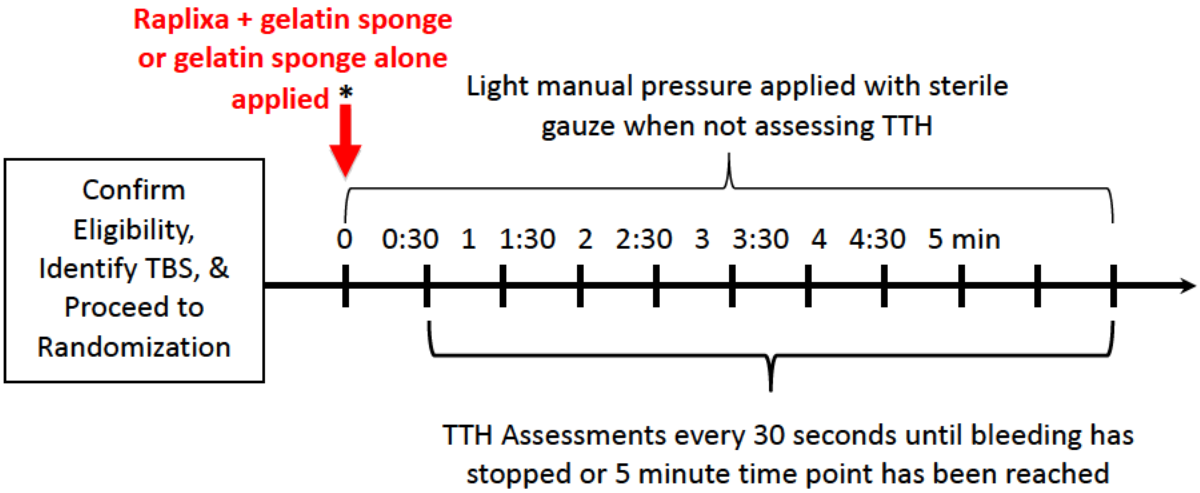
A subject's study participation ends after the Day 30 visit. However, should a subject return to the investigator between Day 30 and Day 90 for routine follow-up visits (not scheduled for the purpose of the study), the investigator will record any update in the subject's safety information and report such information to the Sponsor using the data collection forms provided.

3.2. SCHEMATIC DIAGRAM OF TRIAL DESIGN

Figure 1 Study Schema and TTH Assessment on Visit 2 (Day 1)



*TTH Assessment



3.3. ENDPOINTS

The study endpoints are:

Safety

- Overall safety, as determined by the incidence, severity and relationship of adverse events (AEs) with a study product or a study procedure, clinical laboratory abnormalities, estimated rates of immunogenicity (monitoring for anti-thrombin antibodies) collected and analyzed at baseline and at Day 30 for all treated subjects, except subjects who are less than 6 months old. Additional monitoring for anti-fibrinogen antibodies will be limited to subjects found positive for anti-thrombin antibodies and subjects with unexplained bleeding or clinical suspicion of bleeding related to antibody formation and post-surgery bleeding complications.

Efficacy

- Percentage/proportion of subjects who reach hemostasis from the first identified TBS within 4 minutes of study drug application.
- Restricted mean TTH (during the 5-minute TTH assessment period).
- Through to Visit 5, EOS visit:
    - Use of alternative hemostatic agents on the TBS.
    - Volume of transfused blood (whole blood, fresh frozen plasma (FFP), cryoprecipitate, platelets, or packed red blood cell (PRBC).
    - Incidence of re-operation for bleeding at the TBS.

3.4. MEASURES TO MINIMIZE/AVOID BIAS

3.4.1. Blinded Study

Sealed, blinded envelopes will be provided by an external statistician, who also holds the randomization lists during the study. Only after the surgeon has identified an appropriate TBS, in the operating room, and notified the study coordinator that the site has been identified and he/she is ready for the treatment designation, will the Investigator/designee open a randomization envelope which corresponds with the type of surgical procedure the subject is undergoing. The time of randomization is subsequently recorded. If a randomization envelope has been opened and the subject does not receive the assigned study drug, this envelope may not be used for another subject.

4. SUBJECT POPULATION

The study will enroll subjects undergoing one of the following surgical procedures:

1. Hepatic Surgery

Hepatic wedge resection or anatomic resection of 1 to 5 contiguous hepatic segments, which may be combined with surgical procedures involving the pancreas, gall bladder, bile duct or intestines. Subjects undergoing living-related liver donation are also eligible.

2. Renal Surgery

Nephrectomy associated with diffuse oozing from the retroperitoneal wall.

3. Soft Tissue Surgery

The TBS will be identified during the soft tissue dissection related to the primary operative procedure. Primary operative procedures include but are not limited to: lower anterior resections, abdominal perineal resections, donor skin graft site (split-thickness-meshed, split-thickness-non-meshed, full thickness, and composite graft) in limited burn patients (up to 40% total body surface area [TBSA]), breast mass excision, cleft lip repair, and hernia repair.

Appropriate soft tissue types will include but will not be limited to: loose areolar tissue, fat, lymphatic tissue/lymph node beds, and muscle. The TBS will not involve parenchymal, gastrointestinal or genitourinary soft tissue, cardiac, lung or brain tissue, as Raplixa has not yet been studied in these tissue types.

4. Spinal Surgery

Scoliosis surgery, cervical, thoracic, or lumbar discectomy, corpectomy, laminectomy, lateral or interbody fusion. Epidural bleeding typically described as oozing, flowing, or pulsatile, and normally requiring topical adjuncts to hemostasis is necessary to be considered eligible. The TBS may not be within a bony cavity or other confined area.

5. Vascular Surgery

All subjects undergoing vascular surgery should be systemically heparinized according to standard procedures. The clamp(s) should be removed to determine if an appropriate TBS with mild to moderate bleeding is present. The clamp(s) should remain off once a TBS is identified and during the treatment and assessment of TTH. If protamine reversal is indicated, it should occur after the 5-minute TTH assessment period is completed, unless a safety concern dictates that it should happen earlier. Appropriate vascular surgical procedures may include, but are not limited to: artificial graft (i.e., polytetrafluoroethylene [PTFE] or Dacron) for hemodialysis access (including revision procedures), hemangiomas, and vascular injuries (peripheral or abdominal). The TBS may not involve the heart or the vessels surrounding the heart.

4.1. NUMBER OF SUBJECTS

Approximately 87 subjects will be evaluated for efficacy and safety at up to 25 centers located in the US.

4.2. INCLUSION CRITERIA

Subjects may be included in the study if they meet all of the following criteria:

1. Subject age is ≥ 36 weeks gestational age at birth (for infants) through < 18 years of age at time of treatment.
2. Subject's legal representative (parent or guardian) has signed an institutional review board (IRB)-approved informed consent document.
3. If a subject is ≥ 7 years old, or appropriate age as defined by local regulations, the subject may be required to have signed an IRB-approved assent document.
4. Subject is scheduled to undergo one of the surgical procedures described in the protocol.
5. If female and of child-bearing potential, subject has a negative pregnancy test on the day of surgery (baseline).
6. If subject is a sexually active male or a sexually active female of child-bearing potential, subject agrees to use a medically accepted form of contraception from the time of consent to completion of all of the follow-up study visits.

During Surgery Inclusion Criteria

1. Presence of mild or moderate bleeding/oozing.
2. TBS surface area of ≤ 100 cm^2.
3. Subject has not received any whole blood, fresh frozen plasma (FFP), cryoprecipitate, or platelets within 24 hours prior to study drug. Packed red blood cell (PRBC) transfusions are allowed.
4. Subject has no intra-operative complication other than bleeding which, in the opinion of the Investigator, may interfere with the assessment of efficacy or safety.

4.3. EXCLUSION CRITERIA

Exclusion Criteria

Subjects will be excluded from the study if any of the following exclusion criteria apply prior to enrollment:

1. Gestational age of < 36 weeks at birth (for infants less than 6 months).
2. Subject has any clinically-significant congenital coagulation disorder (e.g., hemophilia A or B) that may interfere with the assessment of efficacy or pose a safety risk to the subject according to the Investigator.

3. Subject has baseline abnormalities of international normalized ratio (INR) > 2.5 or activated partial thromboplastin time (aPTT) > 100 seconds during screening that are not explained by current drug treatment (e.g., warfarin, heparin) or chronic disease state necessitating surgery (e.g., end stage liver disease).
4. Subject has aspartate aminotransferase (ASAT/AST) and alanine aminotransferase (ALAT/ALT) > 3 times the upper limit of reference range during screening, except for subjects undergoing liver resection surgery or with a diagnosis of liver disease where there is no upper limit for these analytes due to the nature of their disease.
5. Subject is unwilling to receive blood products or products derived from human blood
6. Subject has platelets < 100 $x10^9$ PLT/L during screening, unless due to chronic disease state, e.g., liver disease/failure, necessitating surgery.
7. Subject has known antibodies or hypersensitivity to Raplixa or any of its components, other thrombin preparations, or coagulation factors.
8. Subject has known allergy to porcine gelatin.
9. Subject has medical, social, or psychosocial factors that, in the opinion of the Investigator, could impact subject safety or compliance with study procedures.
10. Subject is; 1) currently participating in another clinical study or 2) has participated in another clinical study within 30 days of screening or 3) plans to participate in a clinical study prior to completion of the 30-day follow-up period.

4.4. WITHDRAWAL CRITERIA

Subjects are free to withdraw consent and discontinue participation in the study at any time. If a subject decides to discontinue participation, he/she will be contacted in order to obtain information about the reason(s) for discontinuation and collection of any potential AEs. A subject's participation may be discontinued at any time at the discretion of the Investigator if the subject is uncooperative, major protocol violations or deviations from the treatment plan dictated by the protocol are identified, the Investigator feels that it is in the subject's best interest to be withdrawn from the study, the subject is lost to follow-up after multiple attempts at contacting the subject, or the study is terminated by the sponsor.

A clear, concise reason should be recorded in the electronic case report form (eCRF) for all discontinued subjects. Subjects discontinued from the study due to an AE should be followed until the AE has abated, or is felt to be clinically stable by the Investigator. Follow-up for these subjects may require additional tests or medical procedures as deemed appropriate by the Investigator, and/or referral to the general physician or a medical specialist. All study data from early withdrawals or discontinued subjects will be retained and, if appropriate, used in the final study analyses. Subjects withdrawn or discontinued from the study may be replaced if the statistical powering of the study is impacted.

It is imperative to obtain complete follow-up data for all treated subjects. Every attempt should be made to collect follow-up information except for those subjects who specifically

withdraw consent for release of such information. All procedures and laboratory specimens or tests requested for evaluation following administration of study drug should be carried out when possible, according the protocol. Subjects who are enrolled but not treated with study drug will be withdrawn from the study and may be replaced.

4.4.1. Withdrawal from Study Drug

Due to the nature of treatment there will be no withdrawals from study drug.

4.4.2. Withdrawal from Trial

Reasons that a subject may discontinue participation in this study may include one of the following:

- Adverse event(s).
- Death.
- Subject withdrew consent.
- Physician decision.
- Lost to follow-up.

5. TREATMENT OF SUBJECTS

5.1. STUDY DRUGS

5.1.1. Raplixa

Table 1: Investigational Product

Product Name:	Raplixa™ [Fibrocaps™ (PRO-0601)])]
Dosage Form:	Dry powder
Unit Dose	1.0 g/vial
Route of Administration	Topical
Physical Description	White to off-white powder
Manufacturer	Nova Laboratories, Ltd

Raplixa is a ready-to-use powder consisting of a blend of spray-dried human plasma-derived fibrinogen and thrombin particles with trehalose and calcium chloride with a concentration of 79 mg fibrinogen and 699 international units (IU) thrombin per gram Raplixa (1 vial).

The RaplixaSpray device is classified as a Class II device in the US. The device has been designed and manufactured according to International Organization for Standardization (ISO) 13485:2003 and 21 CFR 820 compliant processes to achieve simple, rapid delivery in the surgical environment onto a bleeding/oozing site. The device complies with the requirements of Medical Device Directive 93/43/EC as revised by 2007/42/EC for investigational devices. The delivery device uses a ball bearing mechanism to mobilize and subsequently deliver Raplixa via the outlet to the target site when the operating button is pressed. A part of this airflow is vented off through the back of the device, while the remaining airflow is used to deliver the Raplixa to the bleeding surface in a narrow plume. The device is supplied with two interchangeable nozzles: one rigid (attached to the device) and one flexible nozzle designed for use in hard to reach bleeding sites. The surgeon may switch the nozzles prior to or during use depending on the location of the bleeding site.

Raplixa Preparation

Prior to surgery, 2 vials of Raplixa and 2 to 3 gelatin sponges will be in the operating room. At sites using the RaplixaSpray device, 2 RaplixaSpray kits that contain the device, flexible nozzle and air filter, one regulator with a hose assembly with site specific connectors (both supplied by the Sponsor), and a central air supply or medical grade pressurized air will be available in the operating room. The second RaplixaSpray device is used as a back-up as needed.

The RaplixaSpray device will be connected to an air filter that is connected to a regulator set to a pressure of 1.5 bar (22 pounds per square inch [psi]), which is connected to either a central air supply or to a tank containing medical grade pressurized air. A vial of Raplixa will

be taken from the packaging in a sterile manner, then uncapped just prior to use and attached to the RaplixaSpray device by inverting the device and connecting the upright vial to the device. The device should be turned upright and the powder visualized in the well of the device prior to use. The application should start within 60 minutes after preparation.

For sites sprinkling Raplixa directly from the vial onto the TBS, the rubber stopper should be removed from the vial just prior to use to prevent the Raplixa from absorbing moisture from the air.

The gelatin sponges will be prepared according to the manufacturers' instructions.

Raplixa Administration

Two vials are allocated for each subject randomized to R+G. One vial (1.0 g) should be used for the initial treatment of the TBS regardless of the mode of administration used. The remaining one vial may be used as needed for the retreatment of the TBS that continues to bleed during the 5-minute TTH assessment period or, after hemostasis at the TBS has been achieved, applied to OBS that are part of the primary operative procedure. Importantly, all of the remaining Raplixa should not be used on OBS until after the 5-minute TTH assessment period has elapsed in order to ensure that adequate Raplixa is available for re-treatment of the TBS if required.

For treating large bleeding surface areas like those frequently encountered during liver and soft tissue surgical procedures, Raplixa is applied topically using the RaplixaSpray device as a thin layer of powder onto the bleeding surface. The device may be used at the discretion of the Investigator for small bleeding sites. The RaplixaSpray device should be held a minimum of 5 cm from the bleeding site when applying Raplixa by pushing the actuator button of the delivery device. Raplixa should be applied accurately and rapidly to the TBS. After Raplixa application, an absorbable gelatin sponge (dry or moistened) is applied, and held in place using light manual pressure with a sterile gauze sponge. Once hemostasis has been achieved, the gelatin sponge may be left in place with the excess carefully removed.

For smaller bleeding surface areas, Raplixa may be applied using the RaplixaSpray device or by sprinkling a thin layer of powder directly from the vial onto the TBS followed by an appropriately-sized gelatin sponge (dry or moistened) and light manual pressure with sterile gauze OR sprinkled directly from the vial onto an appropriately-sized, moistened gelatin sponge that is applied promptly to the TBS followed by light manual pressure applied with sterile gauze. This latter method of application is only appropriate for surgical procedures that have small bleeding surface areas. Once hemostasis has been achieved, the gelatin sponge may be left in place with the excess carefully removed.

The amount of Raplixa used (% of the vial contents) should be estimated and recorded on the eCRF.

5.1.2. Comparator

The control arm consists of Gelfoam® (Absorbable Gelatin Sponge, USP, Pfizer), an approved hemostatic device in the US and is the same as is used with Raplixa. Gelfoam will be provided to the US sites by the Sponsor; however, sites may use their own operating room supply of Gelfoam, if necessary, and must record the name, lot number, and expiration date. The gelatin sponge is cut to the appropriate size and applied topically, dry or moistened, according to the manufacturer's package insert, followed by manual pressure with sterile gauze. If possible, the gelatin sponge should be left in place, while the excess is removed from the bleeding site once hemostasis has been achieved. The appropriately-sized gelatin sponge may be moistened prior to application to the bleeding site, with moistened gelatin sponge recommended for irregularly-shaped bleeding areas. The gelatin sponge should be held in place with light manual pressure using sterile gauze, consistent with manufacturer's directions, and according to the protocol instructions. Subjects may be retreated with gelatin sponge as necessary during the 5-minute observation period. Once hemostasis has been achieved, the gelatin sponge may be left in place with the excess carefully removed.

5.2. PACKAGING AND LABELING

Study drug is provided by the Sponsor. Medication labels will comply with regulatory requirements. The storage conditions for each medication provided will be described on the medication label.

Raplixa raw materials, fibrinogen and thrombin, are supplied by CSL Behring. Raplixa is manufactured under aseptic conditions by Nova Laboratories, Ltd. and the final product labeled by [redacted], according to GMP requirements. Raplixa is packaged in 6 mL type I medical grade glass vials with white aluminum tear-off crimp caps (primary packaging) and a single foil pouch (secondary packaging).

The RaplixaSpray kit consists of a sterilized RaplixaSpray device with rigid nozzle, a sterilized flexible nozzle, and a sterile air filter, which is supplied separately from the Raplixa.

The gelatin sponges will remain in the original packaging labeled with the manufacturer's lot number, and an additional label specifying the clinical trial identification number and Sponsor.

5.3. STORAGE

Raplixa will be shipped to the pharmacy at each study site under controlled temperature with a temperature monitor. Upon receipt the shipment must be stored in a secured area at controlled room temperature (2°C–25°C). The RaplixaSpray kit will be shipped under ambient conditions. Upon receipt, the shipment should be stored in a secured area.

5.4. ACCOUNTABILITY

The Investigator or designee must maintain an inventory record of study drug received and all administered to assure the regulatory authorities and Sponsor that the investigational new drug will not be dispensed to any person who is not a subject under the terms or conditions set forth in this protocol.

The study drug supplied for use in this study is to be prescribed only by the Principal Investigator or designated sub-investigators and may not be used for any purpose other than that outlined in this protocol.

Study supplies will be shipped to the study site following receipt by the Sponsor or designee of written IRB approval and other appropriate study documentation as required.

Study drug and associated supplies are to be tracked and documented from the time of receipt at the site through subject dosing and return to the Sponsor or designee or destroyed at the site (as instructed by the Sponsor). All supplies, including partially used or empty vials, should be tracked. Accountability logs and specific instructions will be provided by the Sponsor or designee and should contain the identification of the subject to whom the drug was dispensed and the date, lot number and quantity of the drug dispensed to the subject. The site may use their own accountability form, if similar information is collected on their form.

All unused vials of study drug are to be retained at the site until inventoried by the Sponsor or designee. All vials used in the operating room may be destroyed, and should be documented. The Sponsor or designee will conduct drug accountability during the course of the study. Disposition of the used study drug during the course of the study should be handled according to the Sponsor's instructions and either disposed of, destroyed at the site, or returned to the Sponsor or designee. Appropriate site standard operating procedures will be followed for destruction of used study drug at the study site.

The Sponsor or designee will conduct final drug accountability at site closure. All used and unused study drug vials should be handled according to the Sponsor's instructions and either returned to the Sponsor or designee, or destroyed at the site.

In the event that study drug needs to be returned for any reason, the site will receive a written request listing the drug lot number(s) to be returned and the reason for the return request.

5.5. CONCOMITANT MEDICATIONS

Subjects may continue all normally prescribed medication regimens during this trial, and must notify the investigator when changes are made to their medication regimens. Medications will be coded using the WHO drug dictionary.

5.5.1. Rescue Treatment

If hemostasis is not achieved TBS during the 5-minute TTH assessment period, administration of additional study drug (no more than 2 vials of Raplixa [2.0 g] total), or other topical hemostats are permitted. If hemostasis cannot be achieved at an OBS or Raplixa is not indicated for use at the OBS, rescue treatment, if needed, should follow a tiered approach:

1. Additional study drug or surgical hemostatic measures (e.g., suture, cautery, and ligature) should be considered first.
2. Followed by thrombin-free topical hemostats.
3. Finally, thrombin-containing hemostats (recombinant or human plasma-derived products) may be administered, if needed.

A list of examples of thrombin-free and thrombin-containing hemostatic agents is provided in Table 2.

Table 2: Examples of Other Topical Hemostatic Agents

Thrombin-Free	Thrombin-Containing[a]
CoSeal™ Surgifoam™ Ultrafoam™ Gelfoam® Instat™ BioGlue® DuraSeal® Bone wax®	CoStasis®/Vitagel™ Crosseal™ Tisseel® Fibrin sealant produced by the blood bank or in the operating room Evicel™ Evithrom™ Recothrom® Surgiflo® Tachosil® Artiss®

a. Investigators should consider the use of products containing thrombin, only after other rescue alternatives fail.

5.6. BLINDING

Subjects will be randomized in a single-blinded manner. Randomization will be done in a 2:1 ratio (active:control).

5.6.1. Blinding of Study Medications

Study drugs will be blinded to study subjects but not to the Investigators, the study site personnel, or the Sponsor's study team.

5.6.2. Method and Maintenance of Blinding

Sealed, blinded envelopes will be provided by an external statistician, who also holds the randomization lists during the study. Only after the surgeon has identified an appropriate TBS, in the operating room, and notified the study coordinator that the site has been identified and he/she is ready for the treatment designation, will the Investigator/designee open a randomization envelope and record the time of randomization. If a randomization envelope has been opened and the subject does not receive the assigned study drug, this envelope may not be used for another subject.

All randomized subjects will be blinded through the end of the study.

6. SCHEDULE AND SEQUENCE OF PROCEDURES

6.1. SCHEDULE OF EVENTS/ASSESSMENTS BY TIME POINT

Table 3: Schedule of Events/Assessments

Visit	1	2	3	4	5
Event	**Screening/Baseline (Days -30 to 1)**	**Surgery (Day 1)**	**Follow-up[a] (16-48 hours post-treatment)**	**Follow-up[i] (Day 7 ± 2 days)**	**EOS[n] (Day 30 ± 7 days)**
Informed Consent/[b]Assent[b]	X				
Inclusion/Exclusion Criteria	X	X			
Medical History	X	X[c]			
Weight, Height	X				
Vital Signs[d]	X	X[e]			X
Physical Examination (PE)	X		X[m]		X[m]
Complete Blood Count (CBC) with differential[f]	X		X		
Blood Chemistry Panel[g]	X		X		
Coagulation Panel[h]	X		X		X
Pregnancy Test[j]		X			
Immunogenicity Sample[k]	X				X
Intra-operative Eligibility		X			
Treatment and TTH Measurement		X			
Documentation of Surgical Procedure		X			
Adverse Events[l]	X	X	X	X	X
Concomitant Medications	X	X	X	X	X

a. For outpatient procedures, Visit 3 may be conducted over the phone with the PE conducted and laboratory tests collected prior to discharge on Day 1.
b. Informed consent and assent (if defined & required by local regulations) may be signed up to 30 days prior to surgery.
c. Review and record any changes in medical conditions since screening visit.
d. Vital signs include resting blood pressure (BP), pulse rate and temperature.
e. Only vital signs, collected pre-operatively.
f. Includes RBC, hemoglobin, hematocrit, platelets and white blood cell (WBC) count with differential.
g. Na, K, blood urea nitrogen (BUN)/urea, Cr, Glu, Alb, AST, ALT, total bilirubin (Tbili).
h. Prothrombin time (PT), aPTT, INR.
i. If the subject has been discharged prior to Day 7, this visit can be a phone call.
j. For females of child-bearing potential only.
k. Immunogenicity samples should not be drawn on infants < 6 months of age.
l. Adverse events are collected from the time of consent.
m. Focused physical examination that is specific for the type of surgery performed and signs and symptoms since the last visit.
n. Study participation ends after the Day 30 visit. However, should a subject return to the investigator between Day 30 and Day 90 for routine follow-up visits (not scheduled for the purpose of the study), the investigator will record any update in the subject's safety information and report such information to the Sponsor using the data collection forms provided.

6.2. GENERAL CONDUCT OF THE TRIAL

Written informed consent will be obtained from subjects' parents/guardians before the performance of any protocol-specific procedure. Further details related to informed consent are found in Section 13.1.

6.2.1. Visit 1: Screening Period (Day –30 to Day 1)

The Screening Visit will take place within 30 days of surgery. Following informed consent, the following screening assessments and procedures will be done:

1. Allocation of a nine digit number, which is composed of the 6-digit site number and incremental subject number.
2. Documentation of:
    a. Demography: date of birth, gender and ethnic origin.
    b. Medical history, including bleeding and surgical history.
    c. Concomitant medications.
    d. Assess and record AEs.
3. Review of inclusion/exclusion criteria to confirm subject eligibility.
4. Blood samples drawn for screening clinical laboratory tests (results may be obtained from clinical laboratory tests measured for routine clinical care prior to consent provided they were measured within 30 days of surgery) and results reviewed prior to enrollment.
    a. Hematology: includes RBC, hemoglobin, hematocrit, platelet count, and white blood cell (WBC) count with differential.
    b. Coagulation: prothrombin time (PT), aPTT, INR.
    c. Blood chemistry panel: sodium, potassium, blood urea nitrogen (BUN)/urea, creatinine, glucose, albumin, AST/ASAT, ALT/ALAT, total bilirubin.
5. Blood sample for immunogenicity testing (do not draw in infants < 6 months old).
6. Physical examination (PE).
7. Weight and height.
8. Vital signs (pulse rate, resting systolic and diastolic blood pressures [BP], and temperature).
9. If a subject is ineligible for the clinical trial, they will be deemed a screen failure and their demographic data and specific reason for ineligibility will be captured on the applicable eCRF page(s).

6.2.2. Visit 2: Surgery, Randomization, and Treatment

Pre-Operative

Pre-operative procedures and assessments include:

1. Review eligibility.
2. Review and record concomitant medications.
3. Assess and record AEs.
4. Measure and record vital signs.
5. Pregnancy Test - only for females of childbearing potential (must document in the subject's source document the reason for the inability to become pregnant).
6. Assess and record changes to baseline health status (changes in health or medical conditions since the screening visit).

Surgery, Randomization and Treatment

The surgery will be carried out according to the local standardized surgical practices; these are not covered within this protocol. Subjects will be randomized after the start of surgery to reduce potential bias.

1. Confirm subject eligibility:
   a. Subject has not received any whole blood, fresh frozen plasma (FFP), cryoprecipitate, or platelets between screening and study drug. Packed red blood cell (PRBC) transfusions are allowed.
   b. There is a TBS with mild or moderate bleeding/oozing. The bleeding intensity will be assessed by the Investigator according to the following description:

      Mild: Oozing and/or capillary leakage

      Moderate: Gradual and steady flow

   c. There are no significant intra-operative complications other than bleeding which, in the opinion of the Investigator, may interfere with assessment of efficacy or safety.
   d. The TBS surface area is ≤ 100 cm^2.

   NOTE: If subjects do not meet these intra-operative criteria, they will be deemed screen failures and their demographic data and specific reason for ineligibility will be captured on appropriate eCRF pages.
2. Randomize subject to treatment group when an eligible TBS is identified. Record the time the subject was randomized.
3. Subject treatment, based on randomization (TTH clock starts as soon as the application of the assigned treatment begins).

a. Raplixa + Gelatin Sponge Group: Rapidly apply Raplixa using one of the following three methods:

   i. Sprinkle a thin layer of Raplixa directly from the vial onto the TBS followed by application of a gelatin sponge (wet or dry).

   ii. Spray a thin layer of Raplixa onto the TBS using the RaplixaSpray device followed by application of a gelatin sponge (wet or dry).

   iii. Apply Raplixa onto a moistened absorbable gelatin sponge that is then applied to the TBS.

   Light manual pressure using sterile gauze should follow for all three application methods.

b. Gelatin Sponge Group: Apply gelatin sponge followed by light manual pressure using sterile gauze.

4. Begin measurement of TTH (Figure 1). Assessment of hemostasis will be made by carefully lifting the sterile gauze pad and checking for bleeding through or around the gelatin sponge. Start the first assessment at 30 seconds and repeat every 30 seconds until hemostasis has been achieved or 5 minutes has elapsed, whichever comes first. In the event that the application takes longer than 30 seconds, the first TTH assessment should commence at the next scheduled time point (i.e., 1 minute).

   a. During this 5-minute assessment period, no further interventions except re-application of Raplixa or a gelatin sponge onto the TBS are allowed, unless the surgeon determines it is medically necessary for the subject's well-being.

   b. When hemostasis has been achieved, record as TTH.

   c. Once TTH has been reached, it is not necessary to continue assessments every 30 seconds, however, the stopwatch should remain running until the end of the 5-minute assessment period.

5. Re-application of Treatment

   Re-application of Raplixa or a gelatin sponge to the TBS being used for TTH assessment is allowed within the 5-minute assessment period if hemostasis has not been achieved. If necessary, the original gelatin sponge should be carefully removed or peeled back to expose the bleeding area to allow the rapid re-application of Raplixa. The entire gelatin sponge may be removed and replaced if necessary.

6. Treatment of Other Bleeding Sites

   At any time after hemostasis has been achieved at the TBS, and the 5-minute TTH assessment period has elapsed, the remaining Raplixa may be used at additional appropriate OBS that are part of the primary surgical procedure. Importantly, the

remaining Raplixa should not be used on an OBS until after the 5-minute assessment period has elapsed in order to ensure that adequate Raplixa is available to use in the event of re-bleeding from the TBS.

Post-Operative Assessments

1. Record the number of Raplixa vials used to treat the TBS and OBS separately.
2. Record the number of RaplixaSpray devices used.
3. Record concomitant medication usage, including blood products. Medications to induce and maintain anesthesia should not be recorded in the eCRF; however, all medications given for treatment-emergent AEs during surgery should be recorded.
4. Assess and record AEs.
5. Focused physical examination and collection of the Visit 3 hematology, coagulation, and blood chemistry samples prior to discharge for subjects undergoing outpatient procedures.

6.2.3. Visit 3: (Day 2, 16-48 hours post-Treatment): Safety Evaluation

Subjects undergoing outpatient procedures may be seen in the office or contacted by phone by study personnel to evaluate the subject's post-operative condition, medication usage and AEs. The following assessments and procedures will be performed on subjects hospitalized at least overnight following their surgery:

1. Focused physical examination.
2. Collect hematology, coagulation panel, and blood chemistry panel samples prior to hospital discharge.
3. Record concomitant medication use, including blood products.
4. Assess and record AEs.

6.2.4. Visit 4: (Day 7 ± 2 days): Safety Evaluation

The following assessments/procedures will be performed via telephone call if the subject has been discharged:

1. Record concomitant medication use, including blood products.
2. Assess and record AEs.

6.2.5. Visit 5: (Day 30 ± 7 days): Safety Evaluation

The following assessments/procedures will be performed:

1. Physical examination.
2. Vital signs.
3. Collect coagulation panel.

4. Collect a blood sample for immunogenicity testing (Note: Should not be collected in infants < 6 months of age).
5. Record concomitant medication use, including blood products.
6. Assess and record AEs.

Study participation ends after the Day 30 visit. However, should a subject return to the investigator between Day 30 and Day 90 for routine follow-up visits (not scheduled for the purpose of the study), the investigator will record any update in the subject's safety information and report such information to the Sponsor using the data collection forms provided.

6.3. STUDY TERMINATION

The Sponsor reserves the right to terminate the study at any time. In terminating the study, the Sponsor and the Investigator(s) will ensure that adequate consideration is given to the protection of the subjects' interests. If the study is terminated, the subject(s) will be followed for all safety assessments up to the EOS visit. Should the study/center(s) be closed prematurely, all study materials (except for study documentation that must remain on site) must be returned to the Sponsor. The Investigator will retain all study documentation until notification is given by the Sponsor for its destruction.

7. PROTOCOL ASSESSMENTS

Demographics, medical history, and baseline demographic information will be collected during screening, and will include age, sex and race/ethnicity.

Medical history (MH) includes all ongoing medical or surgical issues. Remote medical and surgical history > 5 years from the time of screening should only be included if considered relevant to the current surgery (e.g., previous similar surgery and outcomes) or the mechanism of action of Raplixa (e.g., history of thromboembolic events, bleeding events or other coagulation disorders). The MH should also include all prescription medications that the subject is currently taking at the time of Informed Consent. Those medications that are related to the mechanism of action of Raplixa (e.g., previous thrombin or fibrin sealant treatment) within the past 30 days should also be collected. Vitamins and other nutritional supplements need not be recorded since they are not expected to affect the subject's safety or the efficacy of Raplixa during the trial.

7.1. ASSESSMENT OF SAFETY

7.1.1. Adverse Events

Subjects will be carefully monitored for adverse events by the Investigator during the designated study period (see Section 8 for details).

7.1.2. Vital Signs

Vital signs include resting blood pressures, pulse rate and temperature.

7.1.3. Physical Examination

The targeted physical examination should include a focused examination relating to the subject's medical history and current surgical plans. During follow-up, the examination should include the surgical site, which may include general, respiratory, cardiovascular, abdominal, extremities and brief neurologic evaluations as appropriate. Recording of the height and weight should occur at baseline only.

7.1.4. Laboratory Assessments

The laboratory assessments will be collected according to the Schedule of Assessments (Table 3).

Hematology - Complete Blood Count (CBC) with Differential:

Includes RBC, hemoglobin, hematocrit, platelet count, and white blood cell (WBC) count with differential.

Blood Chemistry:

Includes sodium, potassium, BUN/urea, creatinine, glucose, albumin, AST/ASAT, ALT/ALAT, and total bilirubin.

Coagulation Panel:

Includes PT, aPTT and INR.

Pregnancy Test:

All female subjects of child-bearing potential will have a pregnancy test (serum or urine).

Immunogenicity Sample:

This blood sample will be used for measuring anti-thrombin and anti-fibrinogen antibodies in plasma from all subjects treated in the study. An immunogenicity sample should not be collected in infants < 6 months of age due to immature immune system which is indicative of the presence of maternal antibodies.

7.2. ASSESSMENT OF EFFICACY

7.2.1. Time to Hemostasis (TTH)

A TBS with mild to moderate bleeding and a surface area of ≤ 100 cm^2 will be identified, treated according to the assigned study drug, and used to measure TTH. Study drug should be applied as rapidly as possible to the TBS.

The measurement of TTH will begin at t=0, which is the time R+G study drug application to the TBS is started and will end when hemostasis has been achieved or the 5-minute TTH assessment period ends. If hemostasis has not been achieved within 5 minutes, the subject will be considered a treatment failure and the surgeon will implement additional hemostatic measures, including surgical interventions or the use of alternative topical hemostatic agents or devices. See Section 5.5 for a list of example rescue treatments.

TTH will not be measured at OBS treated with study drug, but whether or not hemostasis was achieved and the approximate amount of study drug used will be recorded as described above.

8. ADVERSE EVENTS

8.1. DEFINITIONS

8.1.1. Adverse Event

Per ICH guidelines section E2A, Adverse Event means any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product/used medical device and which does not necessarily have to have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product/medical device, whether or not considered related to the medicinal product/medical device.

In this study, AEs are collected from the moment the subject is consented. AEs which occur between screening and treatment are always considered unrelated to the study drug and devices, but could be considered protocol related.

For subjects who are considered screen failures (i.e., do not meet all inclusion criteria/exclusion criteria), AEs will not be recorded in the eCRF.

Planned hospital admissions and/or surgical operations for an illness or disease that existed before the drug was given or the subject was treated in a clinical study are not to be considered as AEs.

Adverse events or abnormal test findings will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor/Investigator.

8.1.1.1. AE Severity

The severity of an AE and the relationship to study drug will be assessed by the investigator. The investigator should ensure that any subject experiencing an AE receives appropriate medical support until the event resolves.

AE severity will be assessed according to the grading scale in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.1.1.2. Study Drug Causality

The relationship of an AE to study drug and/or device will be assessed with consideration to the following criteria:

- Temporal relationship to the initiation of study drug.
- Response of the event to withdrawal of study drug.
- AE profile of concomitant therapies.
- Clinical circumstances during which the AE occurred.
- Subject's clinical condition and medical history.

Categorization* of causality will be designated by the investigator as stated below:

1. **Unrelated** - A clinical event, including laboratory test abnormality, reported as an adverse reaction, which lacks a reasonable time sequence between study drug administration and the occurrence of the event(s) or for which medical history, concomitant medications or other drugs provide a more likely explanation. Response to withdrawal of the study drug should not support a relationship between the study drug and the event.
2. **Unlikely related -** A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
3. **Possibly related** - A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the study drug, which may possibly be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Information on study drug withdrawal may be lacking or unclear. Re-challenge information is not required to fulfill this definition.
4. **Definitely related** - A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to study drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The

response to withdrawal of the study drug (de-challenge) should be clinically plausible. The event must be clinically definitive using a satisfactory re-challenge procedure if deemed necessary.

* For the purposes of regulatory reporting, categories '3' and '4' will be considered "related."

8.1.2. Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening, i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred (it does not include an event that, had it occurred in a more severe form, might have caused death),
- Results in a significant, persistent or permanent change, impairment, damage or disruption in the subject's body function/structure, physical activities and/or quality of life,
- Requires in-subject hospitalization or prolongs hospitalization,
- Is a congenital anomaly/birth defect, or
- Is another medically significant event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g., allergic bronchospasm requiring intensive treatment in an emergency department or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse).

A distinction should be drawn between serious and severe AEs. Severity is an estimate or measure of the intensity of an AE, while the criteria for serious AEs are indications of adverse subject outcomes for regulatory reporting purposes. A severe AE need not necessarily be considered serious and a serious AE need not be considered severe. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a myocardial infarction (MI) that may be considered minor could also be an SAE if it prolonged hospitalization.

8.1.3. Adverse Device Effects (ADEs)

ADEs include any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. It also includes any event that is a result of a use error or intentional misuse.

In accordance with 21 CFR 803 in the US, a medical device manufacturer (in this case the sponsor) is required to report to the FDA when it learns that any of its devices may

have caused or contributed to a death or serious injury. The sponsor must also report to the FDA when it becomes aware that its device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Under the FDA Medical Device Reporting Requirements, a Serious Injury/Serious Illness [§803.53(c)(2)] is defined as " an injury or illness that is life threatening, even if temporary in nature; results in permanent impairment of a body function or permanent damage to a body structure; or necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure".

A reportable malfunction of a medical device [§803.3(m)] is defined as "a failure of the device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. A malfunction should be considered reportable if any one of the following is true: the chance of a death or serious injury resulting from a recurrence of the malfunction is not remote; the consequences of the malfunction affect the device in a catastrophic manner that may lead to a death or serious injury; the malfunction causes the device to fail to perform its essential function and compromises the device's therapeutic, monitoring or diagnostic effectiveness which could cause or contribute to a death or serious injury, or other significant adverse device experiences."

An incident for Medical Device Vigilance (MDV) in the European Union is any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject, or user or of other persons or to a serious deterioration in their state of health.

8.1.4. Additional Reporting Requirements

Occurrences of events of overdose, drug misuse and drug abuse are considered "important medical events" that should also be reported within 24 hours using the appropriate reporting form. These events should be reported regardless of their association with other adverse events or serious adverse events.

Abuse of a medicinal product: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects [DIR 2001/83/EC Art 1(16)].

Medication error: Refers to any unintended error in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional,

patient or consumer. Medication errors are an important cause of morbidity and mortality and many could be prevented or mitigated. They can fall broadly into 4 categories:

1. Wrong medication.
2. Wrong dose (including strength, form, timing, concentration, infusion rate and amount).
3. Wrong route of administration.
4. Wrong patient.

Occurrences of medication errors in a study subject should be reported within 24 hours using the Medication Error/Overdose form. In cases where a medication error results in a serious adverse event, the Serious Adverse Event reporting form should be used to report the SAE. Non-serious AEs associated with medication errors should be reported in AE page in eCRF.

Misuse: Intentional and inappropriate use of a medicinal product/device not in accordance with the prescribed or authorized dose, route of administration, and/or the indication(s) or not within the legal status of its supply (e.g., without prescription for medicinal products subject to medical prescription).

Overdose: Administration of a quantity of a medicinal product given per administration or per day which is above the maximum recommended dose according to the reference safety information for the investigational product or comparator as applicable. This also takes into account cumulative effects due to overdose.

8.1.5. Adverse Event of Special Interest (AESIs)

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's product or program, which warrants ongoing monitoring and rapid communication by the investigator to the Sponsor (Section 8.6).

8.1.6. Complications of the Disease Under Study

Certain symptoms are considered typical outcomes following surgery and thus are expected side effects. Clinical events that are considered standard post-operative occurrences will be reported as AEs if they are considered untoward or unfavorable. In cases where the event is not considered as untoward or unfavorable it must be recorded as such in the source document. Consistency in reporting adverse events from all participating sites will be ensured through appropriate training and monitoring and investigators will be required to report all untoward or unfavorable events as adverse events based on their clinical judgment.

8.2. PROCEDURE FOR NON-SERIOUS ADVERSE EVENT RECORDING

All non-serious AEs that occur during the designated study period from consent up to EOS visit (Day 30 ± 7 days) following study drug administration must be assessed and recorded on the source documents and eCRF regardless of causal relationship to the study drug.

Study participation ends after the Day 30 visit. However, should a subject return to the investigator between Day 30 and Day 90 for routine follow-up visits (not scheduled for the purpose of the study), the investigator will record any update in the subject's safety information and report such information to the Sponsor using the data collection forms provided.

8.3. PROCEDURE FOR SERIOUS ADVERSE EVENT REPORTING

All SAEs involving the study biologics, the reportable malfunctions, serious injuries, death and incidents involving the biologic-application devices that occur during the designated study period from consent up to 90 days following study drug administration must be reported to Mallinckrodt Pharmaceutical's Global Pharmacovigilance Department (GPV) within 24 hours of awareness of the event using the provided study specific SAE/AESI Report Form and Device Reporting Form, respectively. The completion and processing of the Reporting Forms should follow the instructions in the provided Report Form completion guidelines. In addition to completing the Report Forms, each SAE/AESI, Medical Device Reporting (MDR) reportable malfunction, serious injury, death or Medical Device Vigilance (MDV) incident must be entered on the appropriate page of the CRF.

When death occurs due to a SAE, the cause of death must be reported as the SAE. The outcome of the causal SAE should be designated as "fatal."

The investigator must assess the causality for each SAE and incident.

The Sponsor or its representative will contact the investigator, if necessary, to clarify any of the event information. The investigator should provide any follow-up information for the event to the Sponsor on an SAE/AESI Report Form or a Device Reporting Form as soon as it becomes available.

If the investigator becomes aware of a SAE that occurs post-study period, that he or she wishes to report to the Sponsor (e.g., an event suspected to be causally related to the study biologics or the application devices), the event should be reported through the process described above as soon as possible.

Where appropriate, if required by local regulations or procedures, the investigator should report these events to the Institutional Review Board (IRB)/Ethics Committee (EC) and/or appropriate regulatory authority in addition to the Sponsor.

8.4. PROCEDURE FOR MEDICATION ERROR REPORTING

Medication errors with or without an AE should be recorded as medication errors in the eCRF as described in Section 8.2.

Medication errors with a SAE should be recorded as medication errors in the eCRF and reported to the Sponsor Pharmacovigilance Department as described in Section 8.3.

A missing dose (refer to Section 12.3) should be reported as a medication error if it was an "unintended error" as defined in Section 8.1.4.

8.5. PROCEDURE FOR ADVERSE DEVICE EFFECTS (ADES) REPORTING

Any AE related to the use of an investigational medical device should be reported within 24 hours using the Device Incident Report Form. In cases where an ADE occurs with a Serious Adverse Event, the SAE/AESI Report Form should be used to report the SAE and the Device Report Form should be used to report the ADE. When an ADE occurs without any concurrent SAE, the Device Report Form may be submitted alone.

8.6. ADVERSE EVENTS OF SPECIAL INTEREST

The AESI(s) listed below have been identified for the study product(s) in this protocol. Non-serious AESIs should be reported from the site to the sponsor within 72 hours and serious AESIs should be reported from the site to the sponsor within 24 hours. In both instances, the reporting procedure provided in Section 8.3 should be followed. The SAE/AESI Report Form, along with a targeted questionnaire when applicable, should be utilized for reporting the AESI even if a serious outcome may not apply. The SAE/AESI report form should indicate that the reported event is an AESI.

AESIs for this study product/protocol are as follows:

- Surgical site-related events, which includes inflammation, pain, foreign body reaction, and infection suggestive of a higher complication rate.
- Thromboembolic events, which includes acute ischemic events like pulmonary embolism, myocardial infarction, deep vein thrombosis and stroke.
- Re-bleeding at the TBS, including post-procedural hemorrhage, hematomas and compression/obstruction of the adjacent structures secondary to the hematomas.
- Air emboli-associated events, which includes acute respiratory failure or cardiovascular collapse occurring intra-operatively during or following the use of the RaplixaSpray device.
    - Additional information will be collected for events of potential air/gas emboli using the Raplixa Air or Gas Embolism Adverse Events questionnaire.

- Blood-borne pathogenic diseases such as hepatitis/HIV infection or prion disease suggestive of viral or prion transmission from Raplixa.

8.7. REPORTING EVENTS OF PREGNANCY/LACTATION

Occurrences of pregnancy/lactation exposure in a study subject or study subject's partner should also be reported within 24 hours using the Pregnancy Reporting form. In cases where a pregnancy occurs with a Serious Adverse Event, the SAE/AESI Report form should be used to report the SAE and the Pregnancy Reporting form should be used to report the pregnancy. When a pregnancy occurs without any concurrent SAE, the Pregnancy Reporting form may be submitted alone. The pregnancy must be followed through to outcome of pregnancy. Any pregnancy discovered from the time of consent to follow-up must be reported.

8.8. POTENTIAL SAFETY UPDATES WITHIN 90 DAYS OF STUDY PRODUCT APPLICATION

Study participation ends after the Day 30 visit. However, should a subject return to the investigator between Day 30 and Day 90 for routine follow-up visits (not scheduled for the purpose of the study), the investigator will record any update in the subject's safety information and report such information to the Sponsor using the data collection forms provided.

9. DATA COLLECTION

An electronic data capture (EDC) system will be used for this trial. All users will be trained on the technical features of the EDC as well as the content of the eCRF by qualified personnel prior to gaining access to the EDC. A User ID/Password will be granted after training. This ID is not to be shared amongst the study staff. All users must have a unique account to enter or review data. The eCRF should be filled out by the site within 48 hours after a visit. It is not expected that the eCRF will serve as source for any data collected in this trial. If there is a reason for a site to do so, it must be approved by MDCO and documented in the site files.

Prior to the database being locked, the investigator or designee will review, approve and sign/date each completed eCRF. This signature serves as attestation of the Investigator's responsibility for ensuring that all data entered into the eCRF are complete, accurate and authentic. After the end of the trial, a copy of the data will be provided to the site. This copy will contain the final data, an audit trail of activity on the data, and any queries and answers that were posted for data clarification.

A second data lock date will be set to ensure the capture of safety data from routine or unspecified visits after the Day 30 visit but before Day 90.

10. STATISTICAL PLAN

This is a Phase 2, multicenter, randomized, single-blind, controlled trial in pediatric subjects undergoing hepatic, renal, soft tissue, spinal, or vascular surgery. Subjects will be recruited from up to 25 sites in the US. Subjects who qualify for entry into the study will be randomly assigned in a 2:1 ratio to receive either Raplixa plus gelatin sponge (R+G) or gelatin sponge alone (G). The objective of this study is to evaluate the safety and efficacy of Raplixa plus gelatin sponge, as compared to gelatin sponge alone, for achieving hemostasis in pediatric subjects undergoing hepatic, renal, soft tissue, spinal, or vascular surgery.

A separate Statistical Analysis Plan (SAP) document will provide more detailed specifications for data analysis and presentation.

10.1. SAMPLE SIZE

The sample size estimation is based on data from the completed Phase 3 trial (FC-004). Assuming the proportion of subjects achieving hemostasis within 4 minutes in R+G and G are 87% and 60% respectively, approximately 87 pediatric subjects (58 in R+G, 29 in G) will provide approximately 80% power to detect this difference at the one-sided significance level of 0.025 (equivalently, 2-sided significance level of 0.05) based on a chi-square test for 2 proportions.

10.2. RANDOMIZATION

Subjects will be randomized in a 2:1 ratio to the treatment groups R+G and G alone. Sealed, blinded envelopes will be provided by an external statistician, who also holds the randomization lists during the study. Only after the surgeon has identified an appropriate TBS, in the operating room, and notified the study coordinator that the site has been identified and he/she is ready for the treatment designation, will the Investigator/designee open a randomization envelope and record the time of randomization. If a randomization envelope has been opened and the subject does not receive the assigned study drug, this envelope may not be used for another subject.

10.3. GENERAL STATISTICAL CONSIDERATIONS AND DEFINITIONS

10.3.1. General Statistical Methods

All study-collected data will be summarized by treatment group using descriptive statistics, graphs, and/or raw data listings. Descriptive statistics for continuous variables will include number of subjects (n), mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum (min) and maximum (max) values. Analysis of categorical variables will include frequency and percentage. For time-to-event endpoints such as TTH, the Kaplan-Meier method will be used to estimate the survival distribution for each treatment group.

10.3.2. Analysis Populations

Two subject populations will be used for data analyses and/or presentations.

10.3.2.1. Intent-to-Treat (ITT) Population

The ITT population consists of all randomized subjects. This population will be the primary population for the efficacy analyses.

10.3.2.2. Safety Population

The safety population consists of all subjects who are exposed to any amount of study drug. Treatment classification will be based on the actual treatment received. This will be the primary population for the safety analyses.

10.3.3. Analysis Windows and Baseline

The observational period for the study includes Visit 1 (screening/baseline from Day -30 to Day 1), to Visit 5 (Day 30 ±7 days, End of Study). An additional unscheduled observational period between Days 30 and 90 will be used to collect safety data from routine follow-up visits (not scheduled for the purpose of the study), if any such data were to be captured. Any event occurring after the defined observational period, even if collected on the eCRF, will not be included in the planned statistical analysis. However, all data, including that reported after the defined observational period, will be included in the subject data listings.

Unless otherwise specified, for evaluations that are collected at multiple occasions prior to initiation of study drug, the latest evaluation will be considered the "Baseline" evaluation for analysis.

10.3.4. Missing Data Handling

Unless otherwise specified, missing data will not be imputed and will be excluded from the associated analysis.

10.4. STATISTICAL ANALYSES

Summaries by treatment group will represent subject data across study sites. Descriptive statistics, graphs, and subject data listings will be used to summarize the data collected. For continuous variables, descriptive statistics will include the number of subjects reflected in the calculation (n), mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum (min), and maximum (max). Frequencies and percentages will be displayed for categorical data. Subject data listings will be presented by study sites, treatment group, surgery type, age cohort and subject number.

Unless otherwise specified, the primary population for efficacy analyses will be the ITT population; confirmatory analyses for efficacy will be performed using the safety population. All safety analyses will be performed using the safety population.

10.4.1. Demographic and Baseline Characteristics

Demographic variables will include age (continuous and by age cohort), sex, race, height, and weight. Baseline disease characteristics will include reason for surgery and related co-morbidities.

Subject demographics and baseline characteristics will be summarized by treatment group using the evaluable and safety populations.

10.4.2. Prior and Concomitant Medications

Summaries of each prior (pre-baseline) medication and concomitant (baseline or later) medication will be provided by treatment. Medications will be coded using the WHO Drug Dictionary. Subjects will be counted only once within each period by medication.

10.4.3. Safety Analysis

Overall safety, as determined by the incidence, severity and relationship of adverse events (AEs), clinical laboratory abnormalities, estimated rates of immunogenicity (monitoring for anti-thrombin antibodies and additional monitoring for anti-fibrinogen antibodies will be limited to subjects found positive for anti-thrombin antibodies and subjects with unexplained bleeding or clinical suspicion of bleeding related to antibody formation) and post-surgery bleeding complications.

10.4.3.1. Adverse Events

Adverse events (AE) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. An AE (classified as preferred term) occurring during the study will be counted as a treatment emergent AE (TEAE) when it is not present at baseline or present at baseline but increased in severity after the initiation of study drug.

Summaries of the number and percentage of subjects with at least one SAE, MDR reportable events (malfunction, serious injury, or death), or MDV incident, and the number and percentage of subjects with at least one Grade 3, 4, or 5 AE, classified by MedDRA preferred term and system organ class, will be provided.

Adverse events of special interest as listed below will be summarized by treatment group. Details of the AEs of special interest are in Section 8.6:

- Surgical site-related events.
- Thromboembolic events.
- Re-bleeding at the bleeding sites.
- Gas embolism events.
- Blood borne pathogenic diseases suggestive of pathogen transmission from Raplixa.

Listings will be presented for subjects with SAEs/AEs leading to a treatment discontinuation or death.

The estimated rate of immunogenicity will be reported for both treatment arms. No immunogenicity data will be collected for, or reported on, children less than 6 months of age.

10.4.3.2. Laboratory Tests

Laboratory values will be summarized by treatment group, including changes and percent ages of changes from baseline at each time point. Shift tables summarizing the counts and percentages of subjects who were normal at baseline, but became abnormal subsequently will be provided.

10.4.3.3. Vital Signs

Change and percent change from baseline in vital signs will be summarized descriptively at each scheduled time point by treatment group.

10.4.4. Efficacy Analysis

10.4.4.1. Primary Efficacy Endpoints

The primary efficacy endpoint is:

- Proportion of subjects who reach hemostasis at the first identified TBS within 4 minutes of study drug application.

If a subject achieves hemostasis at any point within 4 minutes of study drug application, they will be considered a "success". All other subjects will be considered a "failure".

The primary endpoint will be analyzed with the ITT population. Comparison of the overall response between treatment arms will be made using logistic regression. This will include the estimation of the overall response rates, with 95% confidence intervals, for each treatment arm. Surgical type may also be included in the analysis model as a potential covariate in order further assess the endpoint.

Additional details of this analysis will be described in the SAP.

10.4.4.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Restricted mean TTH (during the 5-minute TTH assessment period)
- Through Visit 5, EOS visit:
    - Use of alternative hemostatic agents on the TBS.
    - Volume of transfused blood (whole blood, fresh frozen plasma (FFP), cryoprecipitate, platelets, or packed red blood cell (PRBC).
    - Incidence of re-operation for bleeding at the TBS.

The analysis of these variables will be described in the SAP.

11. RECORDS RETENTION

FDA regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- At least 2 years following the date on which a Biologics License Application (BLA) is approved by the FDA, or
- Two years after the Sponsor notifies the investigator that no further application is to be filed with the FDA.

Similarly, ICH guidelines require that essential documents be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

To comply with these requirements, the investigator will not dispose of any records relevant to this study without either (1) written permission from the Sponsor or (2) providing an opportunity for the Sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study, including any data clarification forms (DCFs) received from the Sponsor. Such documentation is subject to inspection by the Sponsor or its agents, the FDA and/or other regulatory agencies.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. MONITORING

The Sponsor has ethical, legal and scientific obligations to carefully follow this study in accordance with established research principles and applicable regulations. The investigator, as part of his responsibilities, is expected to cooperate with the Sponsor in ensuring that the study adheres to the protocol and GCP requirements.

As part of a concerted effort to fulfill these obligations, the Sponsor's monitor will visit the center(s) during the study in accordance with the Monitoring Plan set forth for this trial. The investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records/source documents to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

12.2. AUDITING

The Sponsor may conduct audits at the study center(s). Audits will include, but not be limited to, drug supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents. The investigator agrees to permit audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also inspect the investigator during or after the study. The investigator should contact the Sponsor immediately if this occurs, and must permit regulatory authority inspections.

12.3. PROTOCOL DEVIATIONS

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact the Sponsor, or their agent, at the earliest possible time by telephone. This will allow an early joint decision regarding the subject’s continuation in the study. The investigator and the Sponsor will document this decision. The IRB/EC will be informed of all protocol changes by the investigator in accordance with the IRB/EC established procedure. No deviations from the protocol of any type will be made without complying with all the IRB/EC established procedures. Protocol deviations captured in the eCRF will be documented and listed per site and recorded in the Clinical Study Report.

13. ETHICS AND RESPONSIBILITY

This study will be conducted in compliance with the protocol, the Sponsor's standard operating procedures and/or guidelines, the United States Food and Drug Administration (FDA) regulations, the International Conference on Harmonization (ICH) GCP guidelines, the Declaration of Helsinki and other local regulations, as applicable.

13.1. INFORMED CONSENT

Written informed consent will be obtained from parents/guardians for all subjects before any study-related procedures (including any pre-treatment procedures) are performed. Subjects 7 years and older, or of an appropriate age as defined by local regulations, may be required to sign an IRB-approved assent form. The investigator(s) has both ethical and legal responsibility to ensure that each subject (and their guardian or legally authorized representative) being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on a written informed consent form, which shall be approved by the same IRB or EC responsible for approval of this protocol. Each informed consent form shall include the elements required by ICH, Part E6, Section 4.8 and any applicable local regulations. The investigator agrees to obtain approval from the Sponsor of any written informed consent form used in the study, preferably prior to submission to the IRB or EC.

Once the appropriate essential information has been provided to the parents/guardians and the subject (as required) and fully explained by the investigators (or a qualified designee) and it is felt that the parents/guardians and the subject (as required) understands the implications of participating, the parents/guardians and the subject (as required) and the investigator (or designee) shall sign the IRB or EC approved written informed consent form. The parents/guardians and the subject (as required) shall be given a copy of the signed informed consent form, and the original shall be filed appropriately, according to the institution. A second copy may be filed in the subject's medical record, if allowed by the institution.

13.2. INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE

This protocol, the written informed consent and assent forms (if applicable) and any materials presented to subjects shall be submitted to the IRB or EC identified with this responsibility. Notification in writing of approval must come from the IRB or EC chairman or secretary, to the investigator, either as a letter or as a copy of the appropriate section of the IRB or EC meeting minutes where this protocol and associated informed consent form were discussed. The investigator will not participate in the decision. If the investigator is an IRB or EC member, the written approval must indicate such non-participation in the voting session. The investigator will submit status reports to the IRB or EC as required by the governing body. The IRB or EC must be notified by the

investigator in writing of the interruption and/or completion of the study; the investigator must promptly report to the IRB or EC all changes in research (protocol amendments) and will not make such changes without IRB or EC approval, except where necessary to eliminate apparent immediate hazards to human subjects. In cases where it is necessary to eliminate immediate hazards to subjects, the IRB or EC must then be notified of the change as per local requirements. The investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB or EC and must agree to share all such documents and reports with the Sponsor.

14. CONFIDENTIALITY

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. However, authorized regulatory officials and Sponsor personnel will be allowed full access to the records. All medications provided and subject bodily fluids and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor.

Only unique subject numbers in CRFs will identify subjects. Their full names may, however, be made known to a product regulatory agency or other authorized official if necessary.

With respect to the clinical trial data that is received from countries in the European Economic Area and Switzerland, MDCO has certified adherence to the US-European Union (EU) and the US-Swiss Safe Harbor Principles.

15. REFERENCES

1. Cronkite, EP, EL Lozner, and J Deaver. *Use of thrombin and fibrinogen in skin grafting.* 1944, JAMA 124:976-978.
2. Radosevich, M, HI Goubran, and T Burnouf. *Fibrin sealant: scientific rationale, production methods, properties, and current clinical use.* 1997, Vox Sang, Vol. 72(3):133-43.
3. Spotnitz, WD and Burks, S. *Hemostats, Sealants, and Adhesives: Components of the Surgical Toolbox*. 2008, Transfusion 48:1502-1516.
4. EVICEL® US Package Insert, May 2007.
5. TISSEEL US Package Insert, December 2007.
6. TachoSil® US Package Insert, March 2010.
7. Raplixa® US Package Insert, April 2015.
8. Revel-Vilk, S. *The conundrum of neonatal coagulopathy*. 2012, ASH Education Book, Vol 2012, and No.1:450-454.
9. Andrew M., Vegh P., Johnston M., Bowker J., Ofosu F., and Mitchell L. *Maturation of the hemostatic system during childhood*. 1992, Blood, 80:1998-2005.
10. Verhoef C, Singla N, Moneta G, et al. *Fibrocaps for surgical hemostasis: two randomized, controlled Phase II trials.* 2015, J Surg Res, 194:679-87.
11. Bochicchio GV, Gupta N, Porte RJ, et al. *The FINISH-3 trial: a Phase 3, international, randomized, single-blind, controlled trial of topical Fibrocaps in intraoperative surgical hemostasis.* 2015, J Am Coll Surg, 220:70-81.