CLINICAL STUDY PROTOCOL

EFFICACY AND SAFETY OF TRANEXAMIC ACID IN SPINAL FUSION SURGERY

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1. LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Class
BQL	Below limit of quantitation
BUN	Blood urea nitrogen
CI	Confidence Interval
C_{max}	Maximum serum concentration
CFR	Code of Federal Regulations
CRF	Case report form
DVT	Deep vein thrombosis
EBV	Estimated blood volume
ECG	Electrocardiogram
FDA	Food and Drug Administration
FFP	Fresh frozen plasma
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
Hct_0	Hematocrit at -1 h before surgery
Hct_f	Hematocrit at 48 h after wound closure
Hct_{av}	Hematocrit average
HCV	Hepatitis C virus
IC	Informed consent
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
MI	Myocardial infarction
mL	Milliliter(s)
OTC	Over-the-counter
PK	Pharmacokinetic(s)
R	Reference formulation
T	Test formulation

RLD	Reference Listed Drug
RBC	Red blood cell
WBC	White blood cell
SAE	Serious adverse event
TEAE	Treatment-emergent adverse events
V_L	Volume of blood loss

2. STATEMENT OF COMPLIANCE

The study will be conducted in compliance with applicable FDA and ICH rules, regulations, and guidelines and applicable laws and regulations of the locale and country where the study is conducted. The study will be conducted with the approval of a duly constituted institutional review board (IRB) or ethics committee (EC) in accordance with the requirement of 21 CFR 56 - Institutional Review Boards. The nature and risks of the study will be fully explained to each subject and written consent, obtained in accordance with the requirements of 21 CFR 50 and 45 CFR 46 - Protection of Human Subjects. Subjects will be informed of their rights, including the right to withdraw from the study at any time.

The Principal Investigator(s) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

PI Name Title Organization	Date

3. PROTOCOL SYNOPSIS

Protocol Number and Title:	CP-006-2017 – Efficacy and safety of tranexamic acid in spinal fusion surgery
Study Objectives:	The primary objectives of this trial are to assess: 1. Total Blood Loss based on changes in hemoglobin (Blood loss will be calculated by Nadler's and Gross's formulae from the time of admission to hospital until discharge; Hemoglobin and hematocrit concentrations will be measured pre-operatively, post-operatively, and at 24 h and every 24h thereafter until discharge). 2. Incidence of autologous or allogenic blood transfusion, including red blood cells and coagulation components (such as fresh frozen plasma and platelets). Secondary objectives include assessment of: 1. Total measured blood loss (measured intra-operatively and for up to 24 hours post-operatively and every 24 hours up to discharge when the two subfascial drains are removed). Total Blood Loss may be estimated as 3 times cell saver. 2. Number of patients with symptomatic anemia (such as tachycardia, hypotension, presyncope) of <8.0 g/dL hemoglobin, or any hemoglobin <7.0 g/dL, precipitated transfusion. *[Alternatively, allogenic blood transfusion will be considered for hemoglobin <9 g/dL intraoperatively or <8 g/dL post-operatively]* 3. Number of patients with adverse events related to tranexamic acid such as confirmed deep vein thrombosis (DVT), pulmonary embolism (PE), or seizures. 4. Other outcomes will include functional recovery, duration of hospital stay, and wound

	complications (infections, hematomas, and other complications related with surgery).
Number of Sites:	8
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Principal Investigator and Study Site 5:	Philip Yuan, M.D. Memorial Orthopaedic Surgery Group 2760 Atlantic Avenue Long Beach, CA 90806
Principal Investigator and Study Site 6:	Christopher DeWald, M.D. Matthew Colman, MD PIs, Frank Philips, M.D., Sub PI Division of Spine Surgery Rush University Medical Center Chicago IL

Principal Investigator and Study Site 7:	Arvind Dubey, M.D. 438 Elizabeth St, Hobart TAS 7000, Australia Hobart, Tasmania
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Clinical Laboratory:	
Institutional Review Board:	Western Institutional Review Board Research Foundation Address: 1019 39th Ave SE #120, Puyallup, WA 98374 Phone:(360) 252-2500
Test and Reference Products:	**Test Drug:** Exela's Tranexamic Acid Solution for Injection (10 mg/mL), intravenous infusion bags, manufactured and provided by Exela Pharma Sciences, LLC from a single batch / lot will be administered to all randomized subjects. **Placebo:** Inactive ingredient mixture for injection without drug, intravenous infusion bags containing normal saline, manufactured and provided by Exela Pharma Sciences, LLC from a single batch / lot will be administered to all randomized subjects.
Study Design and Duration of Treatment:	This will be a multicenter, randomized, double-blind, parallel group study comparing tranexamic acid (test) to placebo (control) for reduction of perioperative blood loss after complex spinal fusion surgery (defined as T2 to Pelvis/Sacrum and greater than 4 Functional Spinal Units (4 discs/motion segments=5 Vertebral segments)). In addition to test and control treatments, all patients undergoing spinal fusion surgery will receive anesthesia and standard of care for blood loss including colloid/crystalloid fluid replacement and packed red

	cells, if necessary, according to a common multi-institutional protocol. Anesthesia will keep the mean arterial pressure as low as safe for the patient during exposure of surgery (estimated at 60-80 MAP). Patients will be randomized to receive either 30 mg/kg tranexamic acid as a one hour infusion (3 mL/kg) loading dose prior to start of procedure and as an infusion at 3 mg/kg/h (0.3 mL/kg/h) of tranexamic acid throughout the surgery in the test group; or, a one hour infusion at 3 mL/kg of 0.9% saline prior to start of the procedure and an infusion of 0.9% saline at 0.3 mL/kg/h in the control group. The maximum total dose will be 50 mg/kg. The active phase of the study will be until discharge postoperatively for efficacy measurements and at 6 weeks for safety follow-up. The randomization will be open only to the statistician generating the randomization sequence. All PI(s), study conduct and monitoring staff, as well as the subjects will be completely blinded to the treatments except in the case of emergency.
Study Termination	The study will be terminated if ≥5/12 or 10/36 patients enrolled in the study are diagnosed with treatment related serious adverse events.
Phase:	This will be a Phase III study.
Inclusion Criteria:	All adult patients over age eighteen electively undergoing complex spinal fusion surgery (T2 to Pelvis/Sacrum, greater than 4 FSU's (5 vertebral segments or more)) and have a negative serum pregnancy test result at screening, if female, will be eligible.

Exclusion Criteria:	Allergy to tranexamic acid; spinal tumor/intradural pathology; ankylosing spondylitis; acquired disturbance of color vision; pre-operative anemia (Hb <110 in females, Hb <120 in males); refusal of blood products (Jehova's witnesses); pre-operative use of anticoagulant therapy (Coumadin or heparin within 5 days of surgery); fibrinolytic disorders requiring intra-operative antifibrinolytic treatment; hematological disease (thromboembolic events, hemoglobinopathy, coagulopathy, or hemolytic disease); female patients using combination hormonal contraception; patients with history of subarachnoid hemorrhage; patients with serum creatinine levels above ULN
Population:	Up to approximately 150 patients will be enrolled.
Study Duration:	Approximately 2 months, including a screening visit, drug dosing during surgery, and a 6 week follow up.
Study Procedures:	Subjects who meet admission criteria will be assigned sequential numbers beginning with site#-001. A completed subject is a subject who satisfies the admission criteria and who completes all required assessments. When the subjects meet admission criteria and provide written informed consent, they will receive a subject number and be randomized by subject number into one of two treatment arms. They will receive either tranexamic acid or normal saline according to the randomization schedule. Preoperative Visit: Subjects will provide written informed consent and will then undergo pre-operative data collection/screening, including: • Inclusion Exclusion criteria assessment • Diagnosis leading to surgery • Planned procedure

- Schwab Curve type and coronal curve magnitude (Cobb angle)
- Patient age and demography
- Height, Weight, and Body Mass Index
- Number of units of autologous blood donation
- CBC: Hb/Hct/WBC/platelet count (post-autologous donation)
- Coagulation Profile: PT/PTT/INR
- Medical History and Medication Use
- History of Previous Spine Surgery
- Drug / Alcohol / Tobacco Use
- Medication Allergies
- Pregnancy testing (females only)

Surgery, Drug Dosing, and Hospital Stay: Blinded treatments will be administered at an initial dose of 3 mL/kg as a 1-hour infusion using a calibrated infusion pump prior to start of procedure, and as a 0.3 mL/kg/h infusion throughout the surgery. Blood lost during surgery will be collected by subfascial Hemovac drains at the incision site into canisters containing heparinized saline. Volumes collected will be recorded post-surgery and every 24 h thereafter until discharge. Measured Blood Loss will be estimated as 3 times cell saver; estimates will be taken off of the anesthesia record.

The site will provide a person who will collect blood during consult in OR and record variables and measurements on the data collection sheet throughout the entire surgery. Final Measured Blood Loss will be determined post removal of the two subfascial hemovac drains placed during the procedure.

The Total Blood Loss will be estimated based on the hemoglobin content of the blood prior to surgery (mg/dL) and at each of the desired post-surgery time-points (mg/dL). Blood samples for hemoglobin measurement will be collected prior to start of procedure, at the end of the procedure, at 24 h, and every 24 h thereafter until discharge and removal two subfascial drains. Hematocrit analysis will also be conducted on all collected blood samples. The total amounts of fluids infused and amounts of any red blood cell transfusions may be considered, as applicable, in determining the changes in hemoglobin.

In addition, the following data will be recorded:

- Treatment ID
- Details of surgical procedure [Number of vertebrae fused, number of anchors used, and type of anchors used (screws, hooks, or anchors); Number and type of osteotomies performed]
- Any complication prolonging the surgery time or increasing patient blood loss
- Surgery time
- Estimated blood loss peri-operatively (from drainages and absorbent/surgical pads)
- Volume of cell saver delivered
- Units of autologous transfusion and allogenic transfusion
- Units of fresh frozen plasma and platelets administered
- Volume of crystalloids/colloids given

- Urine output
- Location of Hemovac drains and number of drains placed
- Drain output recorded daily
- Length of drain use (uniformly remove drains when output <120 mL/day)
- Length of hospital stay
- Complications of autologous or allogenic transfusion
- Complications of tranexamic acid including renal, hepatic, thromboembolic, and brain/CNS
- Functional recovery assessments will be completed prior to discharge
- Any wound complications for the duration of hospitalization

Follow-up Procedures: Follow-ups on wound complications will be completed minimally at 6 weeks after surgery. Follow-ups on adverse events related to tranexamic acid (such as seizures, DVTs, and PEs) will be reported immediately if they occur.

Adverse events (AEs) will also be monitored by the investigator and/or designated research staff and spontaneous reporting throughout the study.

Confinement: Patients will be confined to the clinic for surgical procedures and recovery as directed by the principal investigator

Study Endpoints: The primary endpoints of this trial are to assess:

1. Total Blood Loss based on changes in hemoglobin (Blood loss will be calculated by Nadler's and Gross's formulae from the time of admission to hospital until discharge; Hemoglobin and hematocrit concentrations will be measured pre-operatively, post-operatively, and at 24 h and every 24h thereafter until discharge).
2. Incidence of autologous or allogenic blood transfusion, including red blood cells and coagulation components (such as fresh frozen plasma and platelets).

The Secondary endpoints include assessment of:

1. Total Measured Blood Loss (measured intra-operatively and for up to 24 hours post-operatively and every 24 hours up to discharge when the two subfascial drains are removed). Total Measured Blood Loss will be estimated as 3 times cell saver.

2. Number of patients with symptomatic anemia (such as tachycardia, hypotension, presyncope) of <8.0 g/dL hemoglobin, or any hemoglobin <7.0 g/dL, precipitated transfusion. *[Alternatively, allogenic blood transfusion will be considered for hemoglobin <9 g/dL intraoperatively or <8 g/dL post-operatively]*

3. Number of patients with adverse events related to tranexamic acid such as confirmed deep vein thrombosis (DVT), pulmonary embolism (PE), or seizures.

4. Other outcomes will include functional recovery, duration of hospital stay, and wound

	complications (infections, hematomas, and other complications related with surgery).
Safety Assessments:	Safety assessments will include monitoring of AEs, and functional recovery assessments, wound complications, length of hospital stay, blood loss, and transfusions.
Statistical Methods:	The primary efficacy variables and continuous secondary efficacy variables will be analysed using Analysis of Covariance (ANCOVA) where one factor is treatment (TXA vs Placebo) and the other factor is Surgeon. The initial analysis will include the interaction between the two factors in order to assess the similarity of effects across surgeons. Significant interaction effects will occur if (for example), TXA works for some surgeons but not for others. The final efficacy analysis will remove the interaction term and control for overall differences between surgeons. Adverse events will be categorized using MedDRA codes. The TXA and placebo groups will be compared using Fisher exact tests of the number of patients with each category of adverse events. The total number of reported adverse events will also be presented.

4. SCHEDULE OF PROCEDURES

Evaluation Procedure	Screening Visit	Day of Surgery	Discharge	Safety Follow-ups			Study Exit or Early Withdrawal[8]
				24 h	Every 24 h until discharge	6 weeks	
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Diagnosis leading to surgery	X						
Planned procedure	X						
Schwab Curve type and coronal curve magnitude (Cobb angle)	X						
Patient age and demography	X						
Medical/Medication Use History	X						
History of previous spine surgery	X						
Height, Weight, Body Mass Index	X						
Number of units of autologous blood donation	X						
CBC: Hb/Hct/WBC/platelet count (post-autologous blood donation)	X						
Coagulation Profile: PT/PTT/INR	X						
Pregnancy Tests[1]	X	X					
Serum Creatinine	X						
Drug / Alcohol /Tobacco Use	X						
Medication Allergies	X						
Physical Examination	X	X					X
Treatment ID		X					
Details of surgical procedure[2]		X					
Surgical complications		X					
Surgery time		X					
Volume of cell saver delivered		X					

Blood Collection[3]		X	X				
Location of Hemovac drains		X					
Length of drain use			X				
Length of hospital stay			X				
Peri-operative Blood Loss Assessments[4]		X	X				
Transfusions[5]		X					
Complications related to transfusions		X	X				
Urine output[6]		X					
Tranexamic acid related complications[7]		X	X	X	X	X	X
Functional recovery assessment		X	X	X	X	X	X
Wound Complications		X	X	X	X	X	X

[1] Females must have a negative serum pregnancy test result at screening and a negative urine test prior to surgery.
[2]Number of vertebrae fused, number of anchors used, and type of anchors used (screws, hooks, or anchors); Number and type of osteotomies performed
[3] Blood for Hb and Hct measurements will be collected pre-surgery, immediately post-surgery, at 24 h and every 24 thereafter until discharge.
[4] Blood lost during surgery will be collected by subfascial Hemovac drains at the incision site into canisters containing heparinized saline. Volumes collected will be recorded post-surgery and every 24 h thereafter until discharge. Total measured blood loss will be estimated as 3X cell saver; estimates will be taken off of the anesthesia record. The site will provide a person who will collect blood during consult in the OR and record variables and measurements on the data collection sheet throughout the entire surgery. Final blood loss will be measured post removal of the two subfascial hemovac drains placed during the procedure.
The total blood loss will be estimated based on the hemoglobin content of the blood prior to surgery (mg/dL), and post-surgery (mg/dL). Blood samples for hemoglobin measurement will be collected prior to start of procedure, at the end of the procedure, at 24 h, and every 24 h thereafter until discharge and removal of the two subfascial drains. Hematocrit analysis will also be conducted on all collected blood samples. The total amounts of fluids infused and amounts of any red blood cell transfusions will be considered, as applicable, in determining the changes in hemoglobin.
[5] Units of autologous transfusion and allogenic transfusion; Units of fresh frozen plasma and platelets administered; Volume of crystalloids/colloids given.
[6] Urine output during surgery.
[7] Symptoms of thromboembolic complications will be followed and recorded. Either radiocontrast venography or pulmonary scintigraphy will be used to confirm deep vein thrombosis or pulmonary emboli. Any observed seizures during the hospital stay will also be recorded and reported.

5. SCHEMATIC OF STUDY DESIGN

CP-006-2017 – Efficacy and safety of tranexamic acid in spinal fusion surgery

- Study Cohort - > Adult patients over age 18 electively undergoing complex spinal fusion surgery (T2 to pelvis/Sacrum, greater than 4 FSU's (5 vertebral segments or more)).

- Arm 1 - > Subjects receiving study drug (treat) (n = 100).
- Arm 2 - > Subjects receiving placebo (control) (n = 50).

- Sample size - > 150 study subjects; randomized 2:1 Treat / Control

- Intervention: Arm1 – Surgery plus study drug
  Arm 2 – Surgery with placebo

6. BACKGROUND INFORMATION

6.1. Background and Literature

Tranexamic acid is a synthetic derivative of the amino acid lysine that inhibits fibrinolysis by competitively inhibiting plasminogen activation, and to a lesser extent, noncompetitively inhibiting plasmin. Tranexamic acid binds to lysine binding sites on plasminogen and plasmin thereby blocking the action of lysine and preventing fibrin clot breakdown. It is used to treat or prevent excessive blood loss during surgery and in various coagulopathies. Following intravenous administration, tranexamic acid has a half-life for the terminal elimination phase of about 2 hours. Urinary excretion is the main route of elimination via glomerular filtration. Overall renal clearance is equal to plasma clearance of 110-116 mL/min, and more than 95% of the dose is excreted in the urine as unchanged drug.

Recently, the intravenous administration of a 1-gram loading dose and 1-gram 8-hour continuous infusion of tranexamic acid has been shown to reduce all-cause mortality and mortality due to blood loss from serious hemorrhagic trauma injuries[1]. The CRASH-2 trial showed that administration of tranexamic acid to adult trauma patients with, or at risk of, significant hemorrhage within 8 hours of injury significantly reduced all-cause mortality with no apparent increase in vascular occlusive events. As a consequence of this trial, tranexamic acid has been incorporated into trauma treatment protocols worldwide. Tranexamic acid was added to the WHO list of essential medicines following the CRASH-2 study. In addition, numerous studies report the benefits and safety of tranexamic acid in cardiac, gynecological, and orthopedic surgeries. Albeit off-label, tranexamic acid is part of the standard of care protocols of several orthopedic surgery centers for total knee-arthroplasty and hip replacement in the United States.

In the United States, FDA approved indications for tranexamic acid, are limited. It is indicated for treatment of patients with hemophilia to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction, and for the treatment of menorrhagia in women.

The current dosage regimen for intravenous tranexamic acid is to administer 10 mg/kg of CYKLOKAPRON intravenously immediately before tooth extraction in patients with hemophilia. Following tooth extraction, intravenous therapy, at a dose of 10 mg/kg, 3 to 4 times daily may be used for 2 to 8 days.[2]

Exela Pharma Sciences has developed Tranexamic Acid Premixed Injection 10 mg/mL in 0.7% sodium chloride (1gram tranexamic acid/100 mL). The pH of the product is 6.5 to 8.0 and the osmolality is approximately 285 mOsmol/kg. Exela is seeking FDA approval and registration for indications related to the reduction of perioperative blood loss.

6.2. Rationale

As stated earlier, the CRASH-2 study established the safety and efficacy of tranexamic acid use in reducing blood loss in trauma situations and numerous reported studies support the safety and efficacy of tranexamic acid use for reduction of blood loss (or transfusions) in cardiac, gynecologic, and orthopedic surgeries. In addition, several surgical centers within the United States use tranexamic acid as part of their standard protocol during total knee-arthroplasty and hip replacement surgeries. However, this use of tranexamic acid is currently off-label. Exela intends to obtain approval for its tranexamic acid product for the indication of "reduction of perioperative blood loss".

Several literature reported studies have shown tranexamic acid to be effective in reducing perioperative blood loss in spinal fusion surgeries. [3-9] However, most of these studies showing efficacy of tranexamic acid in spinal surgery were conducted outside the United States and used varying dosing regimens. For example, one study reported by Shapiro F, et.al., conducted at Childrens Hospital Boston and Harvard Medical School used high doses of tranexamic acid (100 mg/kg administered over 15 min, followed by a 10 mg/kg infusion throughout the surgery).[3] These authors reported that blood loss was reduced by 42% in the tranexamic acid treated group. A Canadian study by Wong J, et.al., reported a 25-30% reduction in blood loss using a 10 mg/kg initial dose

followed by a maintenance infusion of 1 mg/kg/h until skin closure. [4] Another study by Grant JA, et al., compared a tranexamic acid bolus dose of 10 mg/kg followed by a 1 mg/kg/h infusion with a bolus dose of 20 mg/kg followed by a 10 mg/kg/h infusion in patients with idiopathic scoliosis and reported a 50% reduction in blood loss following the high dose.[5] Verma K et al. reported a study plan to compare a low dose tranexamic acid regimen to a high dose tranexamic acid regimen for use in spinal fusion surgeries.[6] A meta-analysis that consolidated the findings of 11 randomized controlled trials which investigated the use of TXA on surgical bleeding in spine surgery concluded that surgical bleeding and transfusion requirements are reduced using TXA and that there is no apparent association with increased incidence of pulmonary embolism, DVT, or MI.[7]

In summary, substantial support for the use of intravenously infused tranexamic acid in the field of spinal surgery exists.[8,9] Exela aims to use the currently approved dosing regimen of "10 mg/kg initial dose followed by 3-4 doses of 10 mg/kg per day" as the basis for the dosing regimen to be used in this study. The maximum dose as per the currently approved dosing regimen is 50 mg/kg (10 mg/kg initial dose + 4 doses of 10 mg/kg per day). The maximum dose to be administered is maintained as 50 mg/kg per day in the current protocol. However, the dosing regimen is modified as "30 mg/kg over 1-hour as an initial dose prior to surgery and an infusion dose of 3 mg/kg/h throughout the surgery up to a maximum of 50 mg/kg".

6.3. Potential Risks and Benefits

6.3.1. Known Potential Risks[2]

Visual abnormalities, often poorly characterized, represent the most frequently reported postmarketing adverse reaction in Sweden. No retinal changes have been reported or noted in eye examinations in patients treated with tranexamic acid for weeks to months in clinical trials.

Convulsions have been reported in association with tranexamic acid treatment, particularly in patients receiving tranexamic acid during

cardiovascular surgery and in patients inadvertently given tranexamic acid into the neuraxial system.

Ureteral obstruction due to clot formation in patients with upper urinary tract bleeding has been reported in patients treated with tranexamic acid.

Gastrointestinal disturbances including nausea, vomiting, and diarrhea may occur but disappear when the dosage is reduced. Allergic dermatitis, giddiness and hypotension have been reported occasionally. Hypotension has been observed when intravenous injection is too rapid. To avoid this response, the solution should be not be injected more rapidly than 100 mg/min.

Thromboembolic events such as deep vein thromboses (DVTs) and pulmonary embolism (PE) are associated with trnexamic acid use.

6.3.2. Known Potential Benefits

Several studies as discussed in Section 6.2 show that tranexamic acid can reduce perioperative blood loss and accidental trauma.

7. TRIAL OBJECTIVES AND PURPOSE

The purpose of this study is to assess the efficacy and safety of tranexamic acid using a dosage regimen similar to that used in the currently approved indication (intravenous therapy of patients with hemophilia during and following tooth extraction) for the reduction of blood loss and minimizing transfusion rates in patients undergoing spinal fusion surgery. This study will be used to support registration and labeling of Exela's Tranexamic Acid products for use in the United States for this indication.

8. TRIAL DESIGN

8.1. Description of Study Design

A schedule of procedures and assessments is displayed in Section 4.

This will be a multicenter, randomized, double-blind, parallel group study comparing tranexamic acid (test) to placebo (control) for reduction of perioperative blood loss after complex spinal fusion surgery (defined as spinal fusion surgery in the T2 to Pelvis/Sacrum area involving more than 4 Functional Spinal Units (4 discs/motion segments=5 Vertebral segments)). In addition to test and control treatments, all patients undergoing spinal fusion surgery will receive anesthesia and standard of care for blood loss including colloid/crystalloid fluid replacement and packed red cells, if necessary, according to a common multi-institutional protocol. Anesthesia will keep the mean arterial pressure as low as safe for the patient during exposure of surgery (estimated at 60-80 MAP). Patients will be randomized to receive either 30 mg/kg tranexamic acid loading dose as a one hour infusion (3 mL/kg) prior to start of procedure and as an infusion at 3 mg/kg/h (0.3 mL/kg/h) of tranexamic acid throughout the surgery in the test group; or, a one hour infusion at 3 mL/kg of 0.9% saline prior to start of the procedure and an infusion of 0.9% saline at 0.3 mL/kg/h in the control group. The maximum dose will be 50 mg/kg.

The active phase of the study will be for the duration of hospital stay postoperatively for efficacy measurements and at 6 weeks for safety follow-up. The randomization will be open only to the statistician generating the randomization sequence. All PI(s), study conduct and monitoring staff, as well as the subjects will be completely blinded to the treatments except in the case of emergency. An analyzable patient is one who satisfies admission criteria and who completes all required assessments.

8.2. Study Endpoints

8.2.1. Primary Endpoints

The primary endpoints of this trial are to assess:

1. Total Blood Loss based on changes in hemoglobin (Blood loss will be calculated by Nadler's and Gross's formulae from the time of admission to hospital until discharge; Hemoglobin and hematocrit concentrations will be measured pre-operatively, post-operatively, and at 24 h and every 24h thereafter until discharge).

2. Incidence of autologous or allogenic blood transfusion, including red blood cells and coagulation components (such as fresh frozen plasma and platelets).

8.2.2. Secondary Endpoints

The Secondary endpoints include assessment of:

1. Total Measured Blood Loss (measured intra-operatively and for up to 24 hours post-operatively and every 24 hours up to discharge when the two subfascial drains are removed). Total Measured Blood Loss will be estimated as 3 times cell saver.

2. Number of patients with symptomatic anemia (such as tachycardia, hypotension, presyncope) of <8.0 g/dL hemoglobin, or any hemoglobin <7.0 g/dL, precipitated transfusion. *[Alternatively, allogenic blood transfusion will be considered for hemoglobin <9 g/dL intraoperatively or <8 g/dL post-operatively]*

3. Number of patients with adverse events related to tranexamic acid such as confirmed deep vein thrombosis (DVT), pulmonary embolism (PE), or seizures.

4. Other outcomes will include functional recovery, duration of hospital stay, and wound complications (infections, hematomas, and other complications related with surgery).

8.3. Study Population

8.3.1. Inclusion Criteria

Subjects must meet the following inclusion criteria:

1. All adult patients (Male or Female) over age eighteen (>18) electively undergoing complex spinal fusion surgery (defined as T2 to Pelvis/Sacrum and greater than 4 Functional Spinal Units (4 discs/motion segments=5 Vertebral segments).

2. Female subjects of childbearing potential with a negative serum (beta human chorionic gonadotropin [HCG]) pregnancy test at screening and urine pregnancy test at each admission; who are not breastfeeding; do not plan to become pregnant during the course of the study; and agree to use an approved method of birth control, such as condoms, foams, jellies, diaphragm, intrauterine device, sexual abstinence for at least 3 months prior to study;

3. Able to provide written informed consent after risks and benefits of the study have been explained;

4. Able to communicate effectively with study personnel.

8.3.2. Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. History or presence of any clinically significant (based on the Investigator's judgment) cardiovascular, respiratory, metabolic, hepatic, gastrointestinal, renal, hematological, dermatological, neurological, or psychiatric disease or condition preventing the use of tranexamic acid as described in this protocol;

2. History of renal failure or elevated creatinine above 1.4;

3. Any diagnosis of spinal tumor or intradural pathology;

4. Diagnosis of ankylosing spondylitits;
5. History or presence of acquired disturbance of color vision;
6. History of seizures;
7. History of thromboembolic event (DVT or PE) within the past year
8. Current use of anticoagulant medications or past medical history leading to an abnormal coagulation profile preoperatively;
9. Subjects diagnosed with fibrinolytic disorders requiring intra-operative antifibrinolytic treatment; hematological disease (thromboembolic events, hemoglobinopathy, coagulopathy, or hemolytic disease).
10. Significant drug sensitivity or significant allergic reaction to any drug, including tranexamic acid, based on the Investigator's judgment;
11. A subject who has donated or lost 450 mL or more blood volume (including plasmaphoresis) or had a transfusion of any product within 3 months prior to the initial study drug administration.
12. Pre-operative anemia (hb <110 in females, Hb <120 in males);
13. Any subject that choses to refuse blood products for ethical or religious purposes (Jehovah's Witness);
14. Current participation in a drug or other investigational research study or participation within 30 days prior to the initial study drug administration.
15. A subject who may not be able to comply with the safety monitoring requirements of this clinical trial or is considered by the investigator, for any reason, to be an unsuitable candidate for the study.

16. Intraoperative cardiovascular, pulmonary, orthopedic, or anesthetic complication such as myocardial infarction, intraoperative fracture, vasopressor support or emergent intubation.

17. Female patients who are using combination hormonal contraception.

18. Patients with history of subarachnoid hemorrhage.

19. Patients with serum creatinine above ULN.

8.3.3. Withdrawal Criteria

Subjects will be discontinued from the study prematurely if:

1. The subject requests to be withdrawn from the study;
2. A need for a concomitant medication prohibited by the protocol arises;
3. The Principal Investigator decides that it is in the subject's best interest;
4. The subject is incompliant with the protocol;
5. The subject experiences an adverse event that requires premature withdrawal.

8.4. Randomization and Blinding

When the subjects meet admission criteria and provide written informed consent, they will receive a subject number and be randomized by subject number into one of two treatment arms. They will receive either tranexamic acid or normal saline according to the randomization schedule. The randomization schedule will be generated prior to study initiation by a statistical programmer. The pharmacy will perform and document the randomization.

Subjects will be treated according to a randomization schedule prepared prior to the start of the study. The investigator site personnel as well as Exela personnel involved in the monitoring or conducting of the trial will be blinded to the trial drug codes (or kit codes), except in the case of an emergency. Trial drug codes will not be available to the above personnel until after the completion of the trial and final data review.

An individual decoding unit containing emergency identification of the kit contents will be provided for each kit.

i. This decoding unit must not be opened unless an actual emergency occurs. The investigator should also make a careful note of the date, time of opening, and the reason.

ii. In the event that a decoding unit is opened, the Exela monitor must be notified immediately by the investigator.

iii. At the conclusion of the trial, all decoding units are to be returned to Exela together with unused drug supplies.

9. STUDY AGENT

9.1. Study Agent(s) Administration

9.1.1. Study Agent(s) Description

Test Drug: Exela's Tranexamic Acid Intravenous Infusion Bags (10 mg/mL), manufactured and provided by Exela Pharma Sciences, LLC from a single batch / lot will be administered to all randomized subjects.

Test Placebo: Inactive ingredient mixture for injection without drug, intravenous infusion bags containing normal saline, manufactured and provided by Exela Pharma Sciences, LLC from a single batch / lot will be administered to all randomized subjects.

9.1.2. Dosing and Administration

Infuse 3 mL/kg over one hour followed by continuous infusion at 0.3 mL/kg for maximum infusion volume of 5 mL/kg.

9.1.3. Formulation, Appearance, Packaging, and Labeling

The trial drugs will be supplied as kits containing seven (7) identically appearing intravenous bags containing 100 mL of an intravenous solution. Each bag will have a label affixed to it which states the kit-number, bag-number, and directions. A single kit will be used for each subject and will contain tranexamic acid infusion bags or saline bags. *[The number of bags per kit can be changed depending on the longest anticipated surgery time and/or the anticipated highest subject weight]*

9.2. Preparation/Handling/Storage/Accountability

9.2.1. Acquisition and Accountability

The Principal Investigator will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much of each test article is dispensed to and used by each individual subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. A Drug Dispensing Form will be provided for this purpose and will be signed by the Principal Investigator at the conclusion of the study.

9.2.2. Product Storage and Stability

Tranexamic Acid Injection (10 mg/mL) should be stored at controlled room temperature (20 – 25 ºC; or 68 – 77 ºF). Under these conditions Tranexamic Acid Injection (10 mg/mL) is stable for 2 years from date of manufacture.

9.2.3. Preparation

Tranexamic Acid Injection (10 mg/mL) is suitable for direct administration and no additional preparation is necessary.

9.2.4. Retention Samples

Retention (reserve) samples of the test formulations will be selected and retained by the Principal Investigator (or Investigational Pharmacist) in a locked, secure pharmacy cabinet in compliance with the individual clinical site SOP requirements.

The retention period is to be at least five years following the date on which a full or abbreviated NDA or supplemental application is approved, or if not approved, at least five years following the completion of a bioavailability/bioequivalence study. To ensure compliance, Exela/SpineMark will conduct a yearly audit. The drugs will be stored under specified conditions in a designated storage area, locked and with limited access. The investigator will be informed by

Exela/SpineMark at the appropriate time when and how to return the retention samples.

10. STUDY PROCEDURES AND SCHEDULE

10.1. Study Procedures/Evaluations

10.1.1. Study Specific Procedures

Vital Signs Assessments

Vital signs will be monitored just prior to and during surgery and any abnormal vital signs result that is considered clinically significant by the Investigator will be recorded as an adverse event.

Physical Examination

A full physical examination will be performed at the screening visit and prior to discharge from the study or at early termination. A full physical examination includes assessment of general appearance and evaluation of dermatological system, head, eyes, ears/nose/throat, neck, lymph nodes, lungs, heart, abdomen, neurological, and musculoskeletal system.

10.2. Laboratory Procedures/Evaluations

10.2.1. Clinical Laboratory Evaluations

Hematology, chemistry including metabolic profile and urinalysis evaluations will be performed at the pre-operative screening visit and prior to discharge from the study. An abnormal clinical laboratory test result that is considered clinically significant by the Investigator will be recorded as an adverse event and follow-up clinical laboratory evaluations may be performed at the discretion of the Investigator.

Hemoglobin content of the collected blood samples will be done by the clinic site or an accredited lab. Hematocrit concentration of the collected blood samples will also be determined.

Clinical chemistry assessments will be done by the clinic site or an accredited lab.

10.2.2. Other Assays or Procedures

No other assays or procedures are planned for this study

10.2.3. Specimen Preparation, Handling, and Storage

Blood samples for hemoglobin measurement will be collected prior to start of procedure, at the end of the procedure, at 24 h, and every 24 h thereafter until discharge. Hematocrit analysis will also be conducted on all collected blood samples.

Blood lost during surgery will be collected by subfascial Hemovac drains at the incision site into canisters containing heparinized saline. Volumes collected will be recorded post-surgery and every 24 h thereafter until discharge and removal of the two subfascial drains.

10.2.4. Specimen Shipment

Each clinical site will have established procedures for sample shipment as necessary.

10.3. Study Schedule

10.3.1. Screening

Prior to surgery, subjects will provide written informed consent and will then undergo pre-operative data collection/screening, including:

- Inclusion Exclusion criteria assessment
- Diagnosis leading to surgery
- Planned procedure

- Schwab Curve type and coronal curve magnitude (Cobb angle)
- Patient age and demography
- Height, Weight, and Body Mass Index
- Number of units of autologous blood donation
- CBC: Hb/Hct/WBC/platelet count (post-autologous donation)
- Coagulation Profile: PT/PTT/INR
- Medical History and Medication Use
- History of Previous Spine Surgery
- Drug / Alcohol / Tobacco Use
- Medication Allergies
- Pregnancy testing (females only)

10.3.2. Pre-Treatment Procedures

A urine pregnancy test will be performed (females only).

10.3.3. Drug Dosing

Blinded treatments will be administered at an initial dose of 3 mL/kg as a one hour infusion using a calibrated infusion pump prior to start of procedure, and as a 0.3 mL/kg/h infusion during surgery up to a maximum infusion volume of 5 mL/kg. Each treatment will be administered by a calibrated infusion pump. The pump's manufacturer, model, and serial number will be recorded on the CRF. The volume infused remains constant regardless of whether the patient is receiving tranexamic acid or saline.

At the termination of the trial, all unused trial medication must be returned to Exela Pharma Sciences. Instructions for the return of trial medication will be provided by Exela at the completion of the trial.

Blood samples for hemoglobin measurement will be collected prior to start of procedure, at the end of the procedure, at 24 h, and every 24 h thereafter until discharge. Hematocrit analysis will also be conducted on all collected blood samples.

The following data will also be recorded:

- Treatment ID
- Details of surgical procedure [Number of vertebrae fused, number of anchors used, and type of anchors used (screws, hooks, or anchors); Number and type of osteotomies performed]
- Any complication prolonging the surgery time or increasing patient blood loss
- Surgery time
- Estimated blood loss peri-operatively (from drainages and absorbent/surgical pads)
- Volume of cell saver delivered
- Units of autologous transfusion and allogenic transfusion
- Units of fresh frozen plasma and platelets administered
- Volume of crystalloids/colloids given
- Urine output
- Location of Hemovac drains and number of drains placed
- Drain output recorded daily
- Length of drain use (uniformly remove drains when output <120 mL/day)
- Length of hospital stay
- Complications of autologous or allogenic transfusion
- Complications of tranexamic acid including renal, hepatic, thromboembolic, and brain/CNS
- Functional recovery assessments will be completed prior to discharge
- Any wound complications for the duration of hospitalization

10.3.4. Follow-Up Procedures

Follow-ups on wound complications and on adverse events related to tranexamic acid (such as seizures, DVTs, and PEs) will be conducted minimally every 24 h during hospital stay and at 6 weeks.

Adverse events (AEs) will also be monitored by the investigator and/or designated research staff and spontaneous reporting throughout the study.

10.3.5. Final Study/Early Termination Visit

Subjects who complete the study will have procedures collected as described in Period 2. If a subject withdraws early from the study, the same information will be collected as follows:

a. A final physical examination will be done.

b. Sitting vital signs blood pressure, pulse, and temperature will be obtained.

c. Specimens for safety laboratory tests will be obtained.

d. The subject will be asked if he/she had any adverse experiences.

If a subject withdraws from the study at any time, either at his or her request or at the Principal Investigator's discretion, the reason(s) for withdrawal will be recorded on the relevant page of the source. All final visit tasks (discharge procedures) will be completed for all subjects who withdraw from the study. Withdrawn subjects may be replaced at the Sponsor's discretion. Subjects withdrawn due to AEs will be monitored until resolution or stabilization of the AE or until 30 days from the initial report of the AE, whichever occurs first.

If a subject is discontinued, the following consistent terminology will be used to capture this information on the CRF:

- Death
- Lost to Follow-up
- Adverse Event
- Non-Compliance with Study Drug
- Physician Decision
- Protocol Violation
- Study termination by Sponsor
- Withdrawal of Consent

10.4. Concomitant Medications, Treatments, and Procedures

The use vitamin K, aspirin or aspirin containing products are prohibited once a subject is entered into this trial. All other concomitant medications are to be recorded.

Any prescription or over-the-counter medication taken during the study will be recorded in the appropriate section of the source document. Any over-the-counter or prescription medications taken during the study will be recorded as a protocol deviation.

10.5. Efficacy Assessments

The primary objectives of this trial are to assess:

1. Total Blood Loss (based on hemoglobin changes).

2. Incidence of autologous or allogenic blood transfusion, including red blood cells and coagulation components (such as fresh frozen plasma and platelets).

Total Blood Loss will be determined using Gross's formula[11] as follows:

$$V_L = EBV \text{ x } \left(\frac{Hct_0 - Hct_f}{Hct_{av}}\right)$$

Where V_L is the volume of total calculated blood loss, EBV is the estimated blood volume from Nadler's formula, Hct_0 is the hematocrit before surgery, Hct_f is the hematocrit at 24 h or discharge/48 h after wound closure and Hct_{av} is the average of Hct_0 and Hct_f.

Nadler's formula[12] is,

Male: $0.3669 \cdot (\text{height})^3 + 0.03219 \cdot (\text{weight}) + 0.6041$, and

Female: $0.3561 \cdot (\text{height})^3 + 0.03308 \cdot (\text{weight}) + 0.1833$,

where, height is in meters and weight is in kilograms.

Secondary efficacy objectives include assessment of:

1. Total measured blood loss (measured intra-operatively and for up to 24 hours post-operatively and every 24 hours up to discharge when the two subfascial drains are removed). Measured Blood Loss will be estimated as 3 times Cell Saver.

2. Number of patients with symptomatic anemia (such as tachycardia, hypotension, presyncope) of <8.0 g/dL hemoglobin, or any hemoglobin <7.0 g/dL, precipitated transfusion. *[Alternatively, allogenic blood transfusion will be considered for hemoglobin <9 g/dL intraoperatively or <8 g/dL post-operatively]*

3. Number of patients with adverse events related to tranexamic acid such as confirmed deep vein thrombosis (DVT), pulmonary embolism (PE), or seizures.

4. Other outcomes will include functional recovery, duration of hospital stay, and wound complications (infections, hematomas, and other complications related with surgery).

10.6. Safety and Other Assessments

Safety assessments will include monitoring of AEs, functional recovery assessments, wound complications, length of hospital stay, blood loss, and transfusions.

Adverse events will be monitored by the observations of the principal investigator and medical staff and/or spontaneous reporting throughout the study.

10.7. Adverse Events and Serious Adverse Events

10.7.1. Definitions

Adverse Event – Any untoward medical occurrence in a clinical investigation subject administered a drug and does not necessarily have a causal relationship with this treatment. An AE can therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Suspected Adverse Reaction – any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Serious Adverse Event (SAE) – Any experience that is fatal or life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, is a congenital anomaly or birth defect, or an important medical 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 in this definition.

Unexpected Adverse Event/Suspected Adverse Reaction – Any adverse event or adverse reaction that is not identified in nature, severity, or frequency in the Product Labeling.[1]

10.7.2. Classification of an Adverse Event

The Principal Investigator will evaluate all AEs as follows:

Seriousness: whether or not the AE is fatal or life threatening, persistent or permanently disabling, requires or prolongs inpatient hospitalization, is a congenital anomaly or an important medical event or requires medical intervention to prevent one of the above outcomes

Action taken: whether or not the AE caused the subject to discontinue the study drug, or use a concomitant medication

Intensity, to be graded as:

DEGREE	DESCRIPTION
Mild	Awareness of signs and symptoms; easily tolerated
Moderate	Discomfort sufficient to interfere, but not prevent daily activity
Severe	Unable to carry out usual activity

Relationship to study drug, to be graded as:

DEGREE	DESCRIPTION
Not related	The experience is clearly related to other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject.
Unlikely	The experience was most likely produced by other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject which do not follow a known response pattern to the trial drug.
Possible	The experience follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the trial drug, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions or concomitant drug administered to the subject.
Probable	The experience follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the trial drug, and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject

Related	The experience follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the trial drug, and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject, and either occurs immediately following trial drug administration, or improves on stopping the drug, or reappears on repeat exposure, or there is a positive reaction at the application site.

10.7.3. Adverse Event and Pregnancy Follow-Up

The Investigator should take all appropriate measures to ensure the safety of the subjects, including referral to a specialist if indicated. The Investigator should follow up on the outcome of any AE (including SAEs) until the event has resolved or stabilized, or until 30 days from the initial report of the AE, whichever occurs first.

Any pregnancy that occurs in a subject or the partner of a subject on study drug must be reported to the Sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth and presence or absence of any birth defects, congenital abnormalities or maternal and/or newborn complications.

Any SAE brought to the attention of the Investigator within 30 days after cessation of study drug should be reported through the SAE reporting process.

10.7.4. Adverse Event Reporting

Any AE (clinical sign, symptom, or disease) temporally associated with the use of this investigational product, whether or not considered related to the investigational product, should be documented on the source document. All AEs reported by the subject or observed by the Principal Investigator will be individually listed. The signs and symptoms, time of onset (24-hour clock), duration, action taken and follow-up procedures will be reported.

10.7.5. Serious Adverse Event Reporting

The Principal Investigator shall document all AEs. He/she must report (by phone, email, etc.) any SAE to the Sponsor or its designee and to any IRB (Institutional Review Board) that has reviewed and is continuing to review the investigation within 24 hours of the first knowledge of the occurrence.
Fatal or life-threatening occurrences in clinical investigations qualify for very rapid reporting. Regulatory agencies should be notified (e.g., by telephone, facsimile transmission, or in writing) as soon as possible but no later than 7 calendar days after first knowledge by the sponsor.

Serious adverse events that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days after first knowledge by the Sponsor that the case meets the minimum criteria for expedited reporting.
For any SAE, the Principal Investigator must notify the contact persons listed below within 24 hours:

Sponsor contact information
Jason Liu, PharmD
1245 Blowing Rock Blvd.
PO box 818 Lenoir, NC 28645
Tel: (828) 758-5474 ext. 181
Email: jliu@exela.us

Aruna Koganti, PhD, MBA
1245 Blowing Rock Blvd.

PO box 818 Lenoir, NC 28645
Tel: (828) 758-5474 ext. 181 Cell: 410-370-2375
Email: akoganti@exela.us

Principal Investigators will be responsible for reporting any SAEs to the Sponsor, who report them to the FDA.

11. STATISTICAL CONSIDERATIONS

11.1. Statistical Hypothesis

The null hypothesis (H0) is that there is no difference between the two groups. The alternative hypothesis (H1) is that the two groups are significantly different.

11.2. Sample Size Determination

Assuming a two-sided alpha level of 0.05, 80% power and estimated mean blood loss of 2000 mL in the control group (with a relatively low estimated standard deviation of 1000 mL due to limitations in the type of surgery and the patient population) a 25% decrease in blood loss in the treated group would require 128 patients (64 per group). Thus, the proposed sample size of 150 patients (100 active and 50 placebo) will allow 14.7% loss to follow-up which should be sufficient considering the relatively small likelihood of loss to follow-up in these patients.

11.3. Populations for Analysis

Up to approximately 150 patients will be enrolled.

The primary analysis population will be a modified Intent to Treat (mITT) population consisting of all subjects receiving an injection of TXA or Placebo.

The secondary analysis population will be a Per Protocol (PP) population consisting of all subjects without major protocol violations (to be

determined by a blinded committee prior to breaking the double-blind code).

The safety population will consist of all subjects receiving an injection of TXA or placebo.

11.4. Statistical Analysis

11.4.1. General Approach

Data from multiple centers are intended to be combined under this protocol so that an adequate number of patients/subjects will be available for analysis.

Comparability of treatment groups based on demographic and baseline characteristics of the patients/subjects will be evaluated by appropriate statistical tests.

All hypothesis-testing analyses will be performed at the two-sided significance level of 5% (α=0.05).

11.4.2. Analysis of Primary Efficacy Endpoint(s)

The primary efficacy variable will be total blood loss as described in Section 10.1. Since blood loss will be measured up to 24 hours after surgery and over the entire period of hospitalization, the primary measure will be the 24-hour level. Blood loss at later time-points will only be considered significant if the 24-hour measure has also reached statistical significance. Due to the hierarchical structure of this analysis, no adjustment for multiplicity will be performed.

The primary efficacy variables and continuous secondary efficacy variables will be analysed using Analysis of Covariance (ANCOVA) where one factor is treatment (TXA vs Placebo) and the other factor is Surgeon. The initial analysis will include the interaction between the

two factors in order to assess the similarity of effects across surgeons. Significant interaction effects will occur if (for example), TXA works for some surgeons but not for others. The final efficacy analysis will remove the interaction term and control for overall differences between surgeons.

11.4.3. Analysis of Secondary Efficacy Endpoint(s)

Secondary efficacy variables will include the following.

1. Blood loss measured as 3 times cell saver.

Also included as secondary efficacy variables will be several outcomes normally treated as adverse events.

1. Incidence of symptomatic anemia as defined in Section 10.1.

Categorical secondary efficacy variables will be similarly analysed using multiple logistic regression analyses. If incidences are low, analyses of interaction effects may not be possible and Cochran-Mantel-Haenszel tests will be used instead.

11.4.4. Safety Analysis

Adverse events will be categorized using MedDRA codes. The TXA and placebo groups will be compared using Fisher exact tests of the number of patients with each category of adverse events. The total number of reported adverse events will also be presented.

11.4.5. Baseline Descriptive Statistics

In general, continuous variables will be analyzed using Student's t test, binary variables will be analyzed using the Fisher exact test and ordered categorical variables will be analyzed using the Wilcoxon rank-sum test.

11.4.6. Planned Interim Analysis

None planned

11.4.7. Sub-Group Analysis

Exploratory subgroup and covariance analyses may also be performed

11.4.8. Tabulation of Individual Participant Data

Tabulations of individual patient data will be included in the final report.

11.4.9. Exploratory Analysis

Exploratory subgroup and covariance analyses may also be performed

12. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

12.1. Informed Consent Process

A properly executed, written informed consent in compliance with Food and Drug Administration (FDA) regulations and Good Clinical Practice (GCP) guidelines will be obtained from each subject prior to entering the study or performing any unusual or non-routine procedure that involve a risk to the subject. The Principal Investigator will submit a copy of the informed consent document to the IRB for review and approval before research subjects are enrolled. The Principal Investigator will provide a copy of the signed informed consent to the subject and a copy will be maintained in the subject's medical record.

The Principal Investigator will provide the IRB with all requisite material, including a copy of the informed consent. The study will not be initiated until the IRB provides written approval of the protocol and the informed consent. Appropriate reports on the progress of this study by the Principal Investigator will be made to the IRB and the Sponsor in accordance with the applicable government regulations and in agreement with policy established by the Sponsor.

12.2. Confidentiality and Privacy

All information provided to the Principal Investigator by the Sponsor or their designees, including non-clinical data, protocols, source documents and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be released in confidence to the IRB. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than to the Sponsor or their designees or in confidence to the IRB, except if required by law.

12.3. Key Roles and Study Governance

Study governance and ethical oversight:

Western Institutional Review Board
Research Foundation
Address: 1019 39th Ave SE #120, Puyallup, WA 98374
Phone:(360) 252-2500

12.4. Safety Oversight

Study safety monitoring will be the primary responsibility of the Sponsor, Exela Pharma Sciences, LLC, and be coordinated with the CRO, SpineMark.

Medical Safety oversight:

Neel Anand, M.D.
Clinical Professor of Surgery
Cedars -Sinai Medical Center
444 South San Vincente Boulevard, Ste 901
Los Angeles, CA 90048

Safety Coordinator:

Tom Juarez
Director, Regulatory and Quality
SpineMark

12.5. Clinical Monitoring

SpineMark or their designee will monitor all aspects of the study with respect to current GCP and standard operating procedures for compliance with applicable federal regulations. These individuals will have access to all records necessary to ensure integrity of the data and will periodically review progress of the study with the Principal Investigator.

12.6. Quality Assurance and Quality Control

All data recorded during the study will be available for audit against source data and for compliance with GCP and specific protocol requirements. Monitoring of the study progress and conduct will be ongoing.

The Principal Investigator will be responsible for the following:

1. Monitoring study conduct to ensure that the rights of subjects are protected;

2. Monitoring study conduct to ensure trial compliance with GCP guidelines; and

3. Monitoring accuracy, completion and verification from source documents of study data.

12.7. Data Handling and Record Keeping

12.7.1. Data Collection and Management Responsibilities

Data collection and management:

SpineMark, Inc. will be responsible for data collection, management, and control per internal Standard Operating Procedures.

Biostatistician: Fred Hoehler, Ph.D

12.7.2. Study Records and Retention Samples

Principal Investigator will keep all study-related documentation in accordance with FDA, GCP guidelines and SOP. At that time, the Principal Investigator will contact the Sponsor regarding further disposition of the study records and retention samples comply with instructions provided by the Sponsor. No property will be disposed of without the consent of the sponsor.

12.8. Protocol Deviations

Protocol deviation will be documented with the study data and reported to the Sponsor on a regular basis.

12.9. Publication and Sharing Policy

Following completion of the study, the data from this study may be considered for reporting at a scientific meeting or for publication in a scientific journal at the sole discretion of the Sponsor. In the case whereby the results of this study are to be published, the Sponsor will be responsible for these activities and will work with the Principal Investigator(s) to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted and other related issues.

12.10. Final Report

A final summary report will be issued to the Sponsor by SpineMark. Where applicable, it will contain a narrative description of the clinical, analytical, pharmacokinetic and statistical procedures used during the conduct of the study. Appropriate tables and graphs will be created to summarize the data.

13. PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	Sep 18, 2017	Initial protocol finalization	N/A
1.1	Nov 21, 2017	Removal of PIs and study sites that have opted out. Change spinal anesthesia to anesthesia	Administrative changes. There is no way to do major surgery under spinal anesthesia, therefore, the change from spinal anesthesia to anesthesia has been made
1.2	Nov 29, 2017	Reduce number of bags per kit from 10 to 7 Table in Section 9.2.1 **Number of Patients** 100 50	Inventory constraints. Correct error in the table in section 9.1.2 to reflect 2:1 TXA:placebo allocation
1.3	Dec 22, 2017	Changes to Primary and Secondary endpoints Additions to Exclusion Criteria Corrections for consistency throughout the protocol	Changes made as per FDA reviewer comments and recommendations
1.4	Mar 23, 2018	Removed instances of hemoglobin and hematocrit measurements on blood collected from drainages Replaced Dr. Verma with Dr. Saigal as PI	Measurements are not necessary. Dr. Verma has resigned from his position at UW.
1.5	May 15, 2018	Replace Dr. Saigal with Dr. Hershman as PI for site 4	UW has dropped out of the study. Massachusetts General

			Hospital with Dr. Hershman as PI will replace UW.
1.6	May 29, 2018	Replace Dr. Thomas Errico with Dr. Aaron Buckland	Dr. Thomas Errico has retired

14. REFERENCES

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15. PRINCIPAL INVESTIGATOR'S STATEMENT AND SPONSOR APPROVAL SIGNATURE

I agree to conduct the study as outline in the protocol and in accordance with the Sponsor's guidelines and Good Clinical Practice requirements.

PI Name Title Organization	Date
PI Name Title Organization	Date
PI Name Title Organization	Date
PI Name Title Organization	Date

Sponsor Approval Signature

Name Title Sponsor Clinical Monitor Exela Pharma Sciences, LLC	Date

Sponsor Quality and Regulatory Approval Signature

Name Title Sponsor Quality and Regulatory Monitor Exela Pharma Sciences, LLC	Date

16. APPENDIX