CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Randomized, Active Comparator-Controlled, Open-Label, Adaptive Design Study to Assess the Safety and Efficacy of Intravenously-Administered SelK2 in Patients Undergoing Total Knee Arthroplasty.
Protocol Amendment #1:	SELK2-00005, version 2.0 Date: May 21, 2019
Original Protocol:	SELK2-00005, version 1.0 Date: September 4, 2018
Drug Name:	SelK2: a function-blocking, humanized anti-PSGL-1 monoclonal antibody
Investigational Phase:	2
Prepared by:	Jonathan Stocker, Ph.D. Russell Rother, Ph.D.
Sponsor:	Tetherex Pharmaceuticals Corporation Jonathan Stocker, Ph.D. Executive Director, Clinical Development 840 Research Parkway, Suite 512 Oklahoma City, OK 73104 Telephone: (919) 819-2112 Email: jstocker@tetherex.com

SIGNATURE PAGE

Clinical Study Protocol: **SELK2-00005**

Protocol Amendment #1 Date: **May 21, 2019**

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Study Title: A Phase 2, Randomized, Active Comparator-Controlled, Open-Label, Adaptive Design Study to Assess the Safety and Efficacy of Intravenously-Administered SelK2 in Patients Undergoing Total Knee Arthroplasty.

The undersigned verify that they have read, understood, and concur with this protocol (SELK2-00005) and will comply with all study procedures defined in the protocol.

21 May 2019
Date

Jonathan Stocker, Ph.D. (signature)
Executive Director, Clinical Development
Tetherex Pharmaceuticals, Corp.
Oklahoma City, OK

Date Principal Investigator (signature)

Principal Investigator (printed name)

PROTOCOL SYNOPSIS

<table>
<tr><td colspan="2">Name of Investigational Product:
SelK2: a function-blocking, humanized anti-PSGL-1 monoclonal antibody</td></tr>
<tr><td>Name of Sponsor Company:
Tetherex Pharmaceuticals Corporation</td><td>Phase of Development:
Phase 2</td></tr>
<tr><td colspan="2">Title of Study: A Phase 2, Randomized, Active Comparator-Controlled, Open-Label, Adaptive Design Study to Assess the Safety and Efficacy of Intravenously-Administered SelK2 in Patients Undergoing Total Knee Arthroplasty.</td></tr>
<tr><td colspan="2">Number of Patients: Approximately 190 patients; with up to 285 patients possible upon activation of the adaptive arm</td></tr>
<tr><td colspan="2">Number of Sites: Approximately 25 clinical sites</td></tr>
<tr><td colspan="2">Study Population: Male and female patients undergoing elective total knee arthroplasty (TKA)</td></tr>
<tr><td colspan="2">Study Duration:
Each patient will participate in the study for up to 13 weeks, including an up to 30-day Screening Phase, 11-day Treatment Phase, and a 45-day Follow-up Phase. The end of the trial will occur when the last study visit (Day 57) is completed for the last patient enrolled into this study.</td></tr>
<tr><td colspan="2">Study Objectives:
The objectives of this study are to:
- Investigate the efficacy of SelK2 as monotherapy in the prevention of VTE (composite of asymptomatic DVT detected by mandatory unilateral venography of the operated leg or confirmed symptomatic DVT, confirmed symptomatic PE or unexplained death) in patients undergoing primary unilateral TKA;
- Assess the incidence of bleeding events (major bleeding events, clinically relevant non-major bleeding events, and minor bleeding events) in patients administered SelK2 and undergoing primary unilateral TKA;
- Assess the overall safety and tolerability of SelK2 in this patient population;
- Further describe the PK and PD of SelK2;
- Evaluate the immunogenicity of single dose SelK2; and
- To evaluate exploratory efficacy endpoints of inflammation and thrombosis.
- Adaptive arm, if activated, assess the efficacy and safety of SelK2 when given in addition to enoxaparin for the prevention of venous thromboembolism (VTE) in patients undergoing primary unilateral TKA.</td></tr>
<tr><td colspan="2">Study Design:
This clinical study is a multi-center, randomized, active comparator-controlled, open-label, adaptive design study to assess the safety and efficacy of SelK2 in the prevention of VTE events in patients undergoing TKA. A total of approximately 190 patients planning to undergo unilateral TKA will be recruited into two arms of the study.

The two arms of the study will enroll patients in a 1:1 ratio (approximately 95 patients in each arm) as shown below:

1.) 7.5 mg/kg SelK2 (IV, single-dose)
2.) Active Comparator (40 mg Enoxaparin, SC, QD)

Patients planning to undergo scheduled TKA under general anesthesia who meet all the inclusion criteria and none of the exclusion criteria will be eligible for randomization into this study. Prior to randomization, a Screening Phase consisting of clinical and laboratory evaluations will occur within 30 days prior to randomization to assess patient eligibility for this study. Upon meeting all criteria, patients will be randomized into this study using a centralized randomization system.</td></tr>
</table>

Following randomization, patients randomized to the SelK2 arm will receive a single dose of 7.5 mg/kg SelK2 via intravenous (IV) administration over a 30-minute time period at least 12 hours but not longer than 24 hours prior to the start of the TKA procedure. Patients randomized to the enoxaparin arm will receive 40 mg enoxaparin administered SC 12 hours after TKA surgery followed by daily injections of 40 mg enoxaparin for at least 9 consecutive days post-surgery and up to the time point of the venography (with the option of giving an additional 40 mg enoxaparin, SC dose 12 hours prior to TKA surgery).

For all patients, the TKA procedure will be done on Study Day 2. Patients will be required to spend at least 2 nights after TKA procedure in the hospital, and patients, at the discretion of the PI, can remain in the hospital at least up to the day of the venography.

All patients will be required to undergo unilateral ascending venography of the operated leg 10 ± 2 days post-surgery (Study Day 11 ± 2 days). After completion of the venogram, patients will be released from the clinical setting, and this will conclude the Treatment Phase of the study.

The Follow-up Phase of this study will consist of two clinic visits on Days 21 and 57 and two follow-up telephone contacts on Days 29 and 43. The final study visit occurs on Day 57 (Day 57/Early Discontinuation Visit).

Data on all asymptomatic deep vein thrombosis (DVT) as determined by venogram and symptomatic clinical VTE will be collected during both Treatment and Follow-up Phases of the study. Bleeding events and other safety and clinical laboratory assessments including exploratory markers of inflammation and thrombosis, coagulation parameters and bleeding events will be performed throughout both the Treatment and Follow-up Phases. Data on all suspected arterial thrombotic events will also be collected. Blood samples will be collected for PK, PD, and immunogenicity analyses.

A Central Independent Adjudication Committee (CIAC) will assess all venograms, symptomatic VTE outcomes (including DVT and PE), bleeding events, suspected stroke, any other suspected arterial thrombotic events, and death. Adjudicators will be blinded to treatment assignment.

A Steering and Safety Committee will conduct ongoing reviews of all safety and efficacy data in an unblinded fashion.

Adaptive Design: The Steering and Safety Committee and Sponsor will review the accumulating efficacy and safety data at planned intervals, and based upon the safety and efficacy profile of SelK2 may decide to modify enrollment by adding a third study arm testing 7.5 mg/kg SelK2 given in addition to enoxaparin (40 mg, SC, QD) and removal of the SelK2 only arm. The two remaining arms will enroll patients in a 2:1 ratio with two patients receiving SelK2 and Enoxaparin for every one patient receiving Enoxaparin only at doses shown below:

1.) 7.5 mg/kg SelK2 (IV, single-dose) and 40 mg Enoxaparin, SC, QD
2.) Active Comparator (40 mg Enoxaparin, SC, QD)

Criteria for Selection of Patients:

Inclusion Criteria:

1. Males or females, between 18 and 80 years of age, inclusive;
2. Females must be non-pregnant and non-lactating, and either postmenopausal (>12 months since last menses) or using highly effective contraceptive measures as defined by the Clinical Trial Facilitation Group (CTFG) guidelines;
3. Males, if engaged in sexual relations with a partner of child-bearing potential, must use highly effective contraceptive measures as defined by the Clinical Trial Facilitation Group (CTFG) guidelines;
4. Planned to undergo elective, primary total unilateral TKA under general anesthesia; and
5. Able to comprehend and willing to give written informed consent.

Exclusion Criteria:

Patients presenting with any of the following will not be included in the study:

1. Body weight <50 kg at Screening;
2. Previous deep vein thrombosis (DVT) of the leg or pulmonary embolism (PE) within the past year;
3. Malignancy within 1 year, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated;
4. Myocardial infarction, transient ischemic attack or stroke within the last 6 months;
5. Patients at increased risk of bleeding because of history of increased bleeding tendency (i.e., history of bleeding diathesis) or any other condition that in the opinion of the Investigator increases risk of bleeding (e.g., recurrent gastrointestinal ulcer) or patients with a history of intracranial or intraocular bleeding;
6. Brain, spinal, or ophthalmologic surgery within the past 3 months;
7. Cockcroft-Gault calculated creatinine clearance <30 mL/min at Screening (central lab will calculate the Cockcroft-Gault value);
8. Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that, in the opinion of the PI, would render a patient unsuitable for inclusion:
   - ALT or AST >1.5x ULN
   - Total bilirubin >1.5x ULN
   - Platelet count <150,000 or recent (over the last 3 months) history of thrombocytopenia (e.g. platelet count <150,000);
9. Positive test for human immunodeficiency virus (HIV; by history of having HIV antibodies), positive hepatitis B (hepatitis B surface antigen [HBsAg]) or hepatitis C (anti-hepatitis C antibody [Anti-HCV]) at Screening;
10. Uncontrolled hypertension as judged by the Investigator;
11. Clinically significant abnormal ECG at Screening, as judged by the Investigator;
12. Active infection;
13. Unable to undergo venography due to a known allergy to the contrast agent, anticipated poor venous access, impaired renal function, or any other reason identified and specified by the PI;
14. Hypersensitivity to enoxaparin or any contraindication listed in the local labeling of enoxaparin;
15. Any underlying condition (e.g., atrial fibrillation, mechanical heart valve, or recent pulmonary embolism) that may lead to the required concomitant use of anticoagulants/antiplatelet agents (e.g., warfarin, dabigatran, rivaroxaban, apixaban, clopidogrel) that may affect study outcome or any other drug influencing coagulation (except low dose aspirin (100 mg or less));
16. Anticipated use of intermittent pneumatic compression devices and/or electrical/mechanical muscle stimulators post TKA procedure;

17. Anticipated use of indwelling intrathecal or epidural catheters;
18. Participation in any other investigational study drug trial in which receipt of an investigational study drug occurred within 60 days prior to Day 1;
19. History of alcoholism or drug addiction within 1 year prior to Screening;
20. Any acute or chronic condition that, in the opinion of the Investigator, would limit the patient's ability to complete and/or participate in this clinical study; or
21. Unwillingness to comply with all study procedures including follow-up visits, as specified by this protocol, or unwillingness to cooperate fully with the Investigator.

Duration of Treatment:

During the Treatment Phase of this study each patient will receive either:

1) A single 7.5 mg/kg dose of SelK2 administered intravenously 12 to 24 hours prior to the initiation of the TKA surgery, or
2) 40 mg dose of enoxaparin (active comparator) administered SC 12 hours after TKA surgery followed by daily injections of 40 mg enoxaparin, SC for at least 9 additional days post-surgery and up to the day of the planned venography (with the option of giving an additional 40 mg enoxaparin, SC dose 12 hours prior to TKA surgery).

Upon activation of the adaptive arm and discontinuation of the SelK2 only arm of the study, during the Treatment Phase each patient will receive either:

1) A single 7.5 mg/kg dose of SelK2 administered intravenously 12 to 24 hours prior to the initiation of the TKA surgery AND 40 mg dose of enoxaparin administered SC 12 hours after TKA surgery followed by daily injections of 40 mg enoxaparin, SC for at least 9 additional days post-surgery and up to the day of the planned venography, or
2) 40 mg dose of enoxaparin (active comparator) administered SC 12 hours after TKA surgery followed by daily injections of 40 mg enoxaparin, SC for at least 9 additional days post-surgery and up to the day of the planned venography (with the option of giving an additional 40 mg enoxaparin, SC dose 12 hours prior to TKA surgery).

Each randomized patient will undergo TKA surgery on the Day 2 of the study. Patients must stay hospital for at least 2 nights after the TKA. A mandatory venogram will be completed on Study Day 11 (± 2 days). Completion of venography will conclude the Treatment Phase of the study. Patients will then enter a Follow-up Phase of the study which will consist of two clinic visits on Days 21 and 57 and follow-up telephone contacts on Days 29 and 43. The final study visit occurs on Day 57 with a complete set of laboratory and safety assessments. Prior to enrollment into the study, a Screening Phase consisting of clinical and laboratory evaluations will occur within 30 days prior to randomization to assess patient's eligibility for this study. Each patient will participate in the study for up to approximately 13 weeks, including an up to 30-day Screening Phase, 11-day Treatment Phase, and a 45-day Follow-up Phase.

Test Product, Dose Preparation, and Mode of Administration:

Study Drug (SelK2): [redacted] Vials are stored refrigerated at 2 to 8°C and protected from light. A pharmacist or designated personnel will compound individual doses of active study drug for patients on a milligram per kilogram basis in a 100 mL infusion bottle or bag of a sterile 0.9% sodium chloride solution (0.9% Sodium Chloride Injection, USP) in accordance with the Pharmacy Manual. Study drug will be administered over 30 minutes by IV infusion.

Active Comparator (Enoxaparin): Commercially available enoxaparin (40 mg in 0.4 mL water

in pre-filled disposable syringes for SC administration) will be provided to the study site pharmacies for use in this study, in accordance with local regulatory requirements. Enoxaparin should be stored in a temperature-controlled environment which is maintained below 25°C; but should not be frozen.

The Pharmacy Manual will provide further details about handling, storage, and mode of administration.

Dose Rationale: [redacted]

Criteria for Evaluation:

Primary Efficacy Endpoints: The primary efficacy outcome is the composite of asymptomatic deep vein thrombosis (DVT) detected by mandatory unilateral venography of the operated leg or confirmed symptomatic DVT, confirmed symptomatic PE or unexplained death during the Treatment Phase. All efficacy endpoint data will be adjudicated by a blinded Central Independent Adjudication Committee.

Exploratory Efficacy Endpoints: The exploratory efficacy outcomes will include measurements of markers of inflammation and thrombosis (hsCRP and D-dimer, respectively) and other possible PD markers of SelK2 efficacy.

PK, PD, and Immunogenicity Evaluations: Samples will be collected during Treatment and Follow-up Phases for evaluation of PK, PD, and immunogenicity.

Safety:

The primary safety outcome is a composite of major bleeding events or clinically relevant non-major bleeding events during the Treatment Phase. The secondary safety outcomes are the incidence of the composite of major, clinically relevant non-major, or minor bleeding events that occur during the Treatment and Follow-up Phases.

Other safety evaluations will include assessment of adverse events, physical examinations, 12-lead ECGs, vital signs (including temperature, respiratory rate, and seated blood pressure and pulse), clinical chemistry laboratory evaluations, additional laboratory evaluations including prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT), hematology panel, urinalysis, and pregnancy test (female patients of child bearing potential only).

Statistical Methods:

Demographic and other patient data will be summarized by treatment group using descriptive statistics.

The primary efficacy comparison will compare the SelK2 only-treated, SelK2 and enoxaparin-treated, and enoxaparin only-treated arms. The difference in the total VTE rate determined during the entire Treatment Phase will be estimated. The 1-sided lower 90% CI of the difference between the SelK2 and enoxaparin groups only arms as well as the difference between the adaptive arm (SelK2 and enoxaparin) and enoxaparin only arms will be calculated and non-inferiority will be concluded if the upper limit of the 90% CI is ≤ 15%. Absolute changes from baseline in levels of high-sensitivity CRP and D-dimer will be assessed. A number of secondary analyses may be conducted to assess the robustness of the primary analysis finding.

SelK2 concentrations will be summarized by descriptive statistics.

Safety will be assessed by reported adverse events, changes from baseline during treatment in vital signs, ECGs, laboratory parameters, and physical examination and will be summarized using descriptive statistics. Adverse events will be coded using the (Medical Dictionary for Regulatory Activities) MedDRA dictionary and summarized by system organ class, preferred term, Investigator causality assessment, and treatment group. Incidence of bleeding events (as adjudicated by CIAC) will be tabulated by treatment group.

Sample Size Considerations:

Assuming that the rate of VTE for the active comparator (enoxaparin) arm of this study will be 25%, it is estimated that a sample size of 76 evaluable patients per arm should give the study 80% power of declaring non-inferiority between the SelK2 only arm and the enoxaparin active comparator arm. This calculation uses a one-sided 90% CI with a non-inferiority margin of 15%. This calculation assumes that the underlying rate of VTE for the SelK2 and enoxaparin arms will be identical at 25% and with the non-inferiority margin set as the midpoint between the expected active therapy response compared with an assumed placebo event rate in this patient population of 55%. Consequently, making the conservative estimate that up to 20% of randomized patients may not have evaluable endpoint data; a total of 95 patients will be enrolled per arm to provide at least 76 endpoint evaluable patients per arm.

Sample Size Considerations for Adaptive Arm:

With the same assumptions as above for the active comparator (enoxaparin) arm of the study event rate, it is estimated that a sample size of 76 evaluable patients in a combination therapy arm of SelK2 and enoxaparin should give the study 80% power of declaring superiority between the SelK2 and enoxaparin and the enoxaparin active comparator arm for an estimated SelK2 and enoxaparin VTE event rate of 6% (a 19% difference between combination treatment effect and active comparator treatment effect). This calculation assumed a two-sided 0.1 alpha, a Pearson Chi-squared test, and a superiority comparison.

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
AUC_{0-336}	Area Under the Concentration-Time Curve from Time 0 to 336 Hours Postdose
$AUC_{0-\infty}$	Area Under the Concentration-Time Curve Extrapolated to Infinity
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CIAC	Central Independent Adjudication Committee
CL	Clearance Rate
C_{last}	Last Observed Concentration
C_{max}	Maximum Observed Concentration
CO_2	Carbon Dioxide
CRNMB	Clinically Relevant Non-Major Bleeding event
CRO	Contract Research Organization
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
eCFR	Electronic Case Report Form
EENT	Eyes/ears/nose/throat
FcRn	Neonatal Fc Receptors
gamma-GT	Gamma Glutamyl Transpeptidase
GCP	Good Clinical Practice
Hb	Hemoglobin
Hct	Hematocrit
HepB	Hepatitis B
HepC	Hepatitis C
HIV	Human Immunodeficiency Virus
hsCRP	High Sensitivity C-Reactive Protein
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT Analysis	Intent-To-Treat Analysis
IV	Intravenous
kDa	Kilodalton
kg	Kilogram
LDH	Lactate Dehydrogenase
Max	Maximum

MB	Major Bleeding event
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MedDRA	Medical Dictionary for Regulatory Activities
PAHA	Primate Anti-Human Antibodies
PD	Pharmacodynamics
PE	Pulmonary Embolism
PK	Pharmacokinetics
PP	Per-Protocol
PSGL-1	P-Selectin Glycoprotein Ligand-1
PT	Prothrombin Time
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SRM	Study Reference Manual
$t_{1/2}$	Terminal Phase Half-Life
TEAE	Treatment-Emergent Adverse Event
TKA	Total Knee Arthroplasty (Total Knee Replacement Surgery)
UA	Urinalysis
VCAM	Vascular Cell Adhesion Molecule
V	Volume of Distribution
VTE	Venous Thromboembolism
V/V	Volume to Volume Ratio
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

1.0 INTRODUCTION

1.1 Background

Deep vein thrombosis and pulmonary embolism are collectively referred to as venous thromboembolism (VTE). Venous thromboembolism is a major medical burden affecting millions of people around the world, with approximately 300,000 deaths and 540,000 deaths annually in the United States and the European Union, respectively. Current therapies available for venous thromboembolism include low-molecular-weight heparins (e.g., enoxaparin sodium), vitamin K antagonists (e.g., warfarin), and newer oral anticoagulants (e.g., rivaroxaban; a factor Xa inhibitor). These therapies target the coagulation system and can therefore result in the feared complication of hemorrhage, which can sometimes be fatal.

VTE is one of the most serious complications experienced by patients undergoing joint replacement surgeries such as total knee arthroplasty (TKA). Following elective TKA, objective venographic evidence of primarily asymptomatic deep vein thrombosis (DVT) occurs in 41-85% of patients without thromboprophylaxis. Because of the strong concordance between asymptomatic DVT detected by venography and clinically important VTE, DVT detected by contrast venography is most often used in the early investigation of new antithrombotic agents (1).

Considering the high incidence of VTE following TKA, the use of routine thromboprophylaxis is recommended in these patients. However, agents available for use in this patient population block the coagulation system and can cause major bleeding events leading to significant morbidity and mortality. There is a continuing medical need for the development of novel antithrombotic agents, especially those that may operate through a unique mechanism of action which is not associated with an increase in bleeding risk.

The relationship between VTE and vein wall inflammation has been well established. PSGL-1 (P-selectin glycoprotein ligand-1) and the selectin family of molecules (P-, E- and L-selectin) are cell adhesion molecules, regulating the interactions between leukocytes, the blood vessel wall, and activated platelets. The importance of PSGL-1/selectin interactions in the inflammatory process leading to VTE has been confirmed in several nonhuman primate studies. Collectively, these studies indicate that inhibition of PSGL-1 interactions with its selectin ligands results in a decrease in thrombosis, and importantly, in the absence of bleeding complications. The level of reduction in thrombosis resulting from PSGL-1/selectin inhibition is similar to that with the low-molecular-weight-heparin, enoxaparin, which is associated with bleeding complications.

During total hip and total knee replacement surgeries, endothelium injury and platelet activation result in the upregulation of selectins and disruption of the regulatory mechanisms of hemostasis. Platelets and the endothelium then participate in the formation of blood clots through receptor interactions with PSGL-1 found on multiple inflammatory cell types. The use of a tourniquet in total knee replacement surgery and immobilization following surgery also induces inflammation and increases the risk of thrombosis.

SelK2 is a humanized monoclonal antibody that binds PSGL-1 with high affinity and specificity and blocks its ability to interact with selectins as well as with chemokines. Because of its ability to block the interactions of PSGL-1 with selectins and chemokines, SelK2 may be useful in the prevention of VTE in patients undergoing TKA.

1.2 Preclinical Studies Supporting SelK2 Antithrombotic Activity

1.2.1 *In Vivo* Mechanism of Action

The vascular anatomy and coagulation system of baboons are similar to those of humans. Therefore, baboon models of VTE and bleeding provide an excellent reflection of what might happen in humans. In one such model of DVT, baboons are subjected to either infrarenal inferior vena cava or iliac vein balloon occlusion with hypogastric vein ligation. In a meta-analysis of five different baboon studies using this model, PSGL-1/selectin inhibition reduced thrombosis to a similar degree as enoxaparin (2). Selectin blockade also successfully reduced vein wall inflammation and fibrosis which has important implications for the prevention of postthrombotic syndrome. Importantly, bleeding was not reported in any study and coagulation parameters were not adversely affected.

In a more recent study conducted in a baboon iliac vein stasis model of DVT, a P-selectin binding aptamer that inhibits PSGL-1/P-selectin interactions was shown to be effective in both prophylactic and treatment applications (3). Selectin inhibition resulted in increased iliac vein recanalization and valve competency equal to or greater than those observed with enoxaparin treatment. Importantly, selectin inhibition decreased intimal fibrosis while enoxaparin did not. There were no significant changes in fibrinogen or activated partial thromboplastin time and no bleeding events were observed in the study.

[redacted]

Collectively, these studies indicate that inhibition of PSGL-1 interaction with its selectin ligands results in a decrease in thrombosis and improvements in both valve competency and vessel patency. The reduction in thrombosis with PSGL-1/selectin inhibition is similar to that with enoxaparin. Further, selectin inhibition results in a decrease in vein wall inflammation and fibrosis with no effect on inflammatory cell extravasation into the vein wall. Importantly, the antithrombotic activity with selectin inhibition occurs in the absence of potential bleeding complications characteristic of anticoagulants (4, 5).

These data suggest that the inflammatory and procoagulant factors involved with thrombus initiation and resolution are associated with PSGL-1/selectin interactions on various cell types and that blockade of these interactions may be a novel therapeutic strategy in the prophylaxis and/or treatment of VTE. Further, intervention of the inflammatory response early in thrombogenesis may be beneficial for prevention of postthrombotic syndrome that often develops following DVT.

1.2.2 Toxicology

[redacted]

[redacted]

[redacted]

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[redacted]

[redacted]

1.2.3 Absorption, Distribution, Metabolism, and Excretion

[redacted]

[redacted]

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1.3 Clinical Studies of SelK2

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1.4 Study Rationale

Venous thromboembolism is a major medical burden affecting millions of people around the world, with approximately one million cases and 300,000 deaths annually in the United States and approximately 1.5 million cases and 540,000 deaths annually in the European Union.

Approved therapies and standard of care available for use in VTE target the coagulation system and can therefore result in major bleeding events leading to significant morbidity and mortality. There is a continuing medical need for the development of novel antithrombotic agents, especially those that may operate through a unique mechanism of action which are not associated with an increase in bleeding risk.

This randomized, active comparator-controlled, open-label study is being conducted to determine the efficacy and safety of SelK2 when administered once to patients undergoing primary unilateral total knee arthroplasty. The study will compare the efficacy and safety of SelK2 to the standard of care, enoxaparin. The primary endpoint to assess clinical efficacy will be the composite of asymptomatic DVT, detected by mandatory unilateral venography, and objectively confirmed symptomatic VTE during the treatment phase of the study. The primary safety outcome is a combination of major bleeding events and clinically relevant non-major bleeding events during the treatment phase.

This study includes an adaptive arm that investigates the efficacy and safety of SelK2 use in combination with enoxaparin. This adaptive arm may be initiated if the Steering and Safety Committee determines that preliminary data suggests the potential of an additive effect in VTE reduction and that the combination does not pose an additional safety risk. The data obtained from this Phase 2 study will be used to provide evidence to support the claim of efficacy and safety of SelK2 in this patient population.

1.5 Rationale for the Dose Regimen

[redacted]

2.0 STUDY OBJECTIVES

The objectives of this study are:

Primary:

- To investigate the efficacy of SelK2 as monotherapy for the prevention of VTE (composite of asymptomatic DVT detected by mandatory unilateral venography of the operated leg or confirmed symptomatic DVT, confirmed symptomatic PE or unexplained death) in patients undergoing primary unilateral TKA.
- To assess the incidence of bleeding events (major bleeding events, clinically relevant non-major bleeding events, and minor bleeding events) in patients administered SelK2 and undergoing primary unilateral TKA.
- To assess the overall safety and tolerability of SelK2 in this patient population.

Secondary:

- To further describe the PK and PD of SelK2.
- To evaluate the immunogenicity of single dose SelK2.
- To evaluate exploratory efficacy endpoints of inflammation and thrombosis.

Adaptive Arm (SelK2 given concomitantly with enoxaparin; SelK2, 7.5 mg/kg, IV and enoxaparin, 40 mg, SC, QD):

- Assess the efficacy and safety of SelK2 when given in addition to enoxaparin for the prevention of VTE in patients undergoing primary unilateral TKA.

3.0 STUDY DESIGN

3.1 Basic Design Characteristics

This trial will be conducted at approximately 25 clinical centers as a multi-center, randomized, active-comparator controlled, open-label, adaptive design study to assess the safety and efficacy of intravenously-administered SelK2 in patients undergoing total knee arthroplasty. A total of approximately 190 male or female patients between the ages of 18 and 80 years, inclusive, who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for the study. After a complete assessment of inclusion and exclusion criteria and prior to the day of surgery, patients will be randomized into one of two arms with a 1:1 ratio (approximately 95 patients in each arm) as below:

1. SelK2 (7.5 mg/kg, IV, single-dose)
2. Active Comparator Enoxaparin (40 mg, SC, QD for up to 10 ± 2 days)

For those randomized to receive SelK2, patients will receive a single dose of 7.5 mg/kg SelK2 via IV administration at least 12 hours but not longer than 24 hours prior to the start of the TKA surgery.

For those randomized to receive enoxaparin, patients will receive their first dose of 40 mg enoxaparin administered SC 12 hours after TKA surgery followed by daily injections of 40 mg enoxaparin for at least 9 additional days post-surgery (with the option of giving an additional 40 mg enoxaparin SC dose 12 hours prior to TKA surgery).

Upon activation of the adaptive arm and discontinuation of the SelK2 only arm of the study, during the Treatment Phase each patient will receive either:

1. A single 7.5 mg/kg dose of SelK2 (7.5 mg/kg, IV, single dose) and Enoxaparin (40 mg SC, QD for up to 10 ± 2 days)
2. Active Comparator Enoxaparin (40 mg, SC, QD for up to 10 ± 2 days)

The TKA will be conducted on Day 2 of the study. All patients will be required to stay in the hospital after TKA and can be released from hospital on Study Day 4 (at the earliest). On Study Day 4, a complete set of safety assessments will be completed on all patients. At 10 ± 2 days post-surgery (Study Day 11), a mandatory unilateral venography will be performed on the operated leg; at that visit a set of safety assessments will also be completed. Upon completion of the venography, patients will continue in the Follow-up Phase for a total of 8 weeks. The Follow-up Phase will consist of two phone call assessments and two safety visits in the clinic including a final safety visit occurring on Study Day 57. The trial will conclude when the last study visit (Day 57) is completed for the last patient enrolled into this study.

3.2 Number of Patients

Approximately 190 patients are planned to be enrolled in this clinical study as designed. Based on adaptive design, if a third cohort of the study is added, an additional 95 patients may be added for a maximum of approximately 285 patients enrolled.

3.3 Study Population

Patients planning to undergo primary unilateral TKA who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for the study. Patients must be willing to undergo all study protocol assessments, tests and activities including unilateral venography of the operated leg approximately 10 days after TKA surgery.

3.4 Study Phases

The study consists of Screening, Treatment and Follow-Up Phases. Each patient will participate in this study for a total of up to 13 weeks, including an up to 30-day Screening Phase, followed by enrollment into the study, a 11-day (± 2 day) Treatment Phase, and a 45-day Follow-up Phase.

3.4.1 Screening Phase

Once informed consent has been obtained, the screening assessments will be performed, and the eligibility of the patient will be determined. During the Screening Phase, clinical and laboratory evaluations will occur within 30 days prior to randomization. A screening log of all patients meeting the inclusion criteria will be maintained. Patients who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for the study. At the Investigator's discretion, patients that are excluded from the study may be rescreened for study inclusion at a later date that is at least two weeks following the initial study exclusion. A patient may become a screen failure if they do not meet all of the inclusion criteria and/or meet one or more of the exclusion criteria. The primary reason for patient exclusions will be recorded for patients who are not randomized.

3.4.2 Treatment Phase

After assessment that the patient has met all Inclusion Criteria and none of the Exclusion Criteria, on the day PRIOR to the scheduled TKA surgery, the patient will be randomized into this study. Prior to dosing of any study drug, baseline safety assessments will be taken.

For those randomized to receive SelK2, patients will receive a single dose of 7.5 mg/kg SelK2 via IV administration at least 12 hours prior to but not longer than 24 hours prior to the start of the TKA surgery. The Treatment Phase of the study consists of the period from the dosing of study drug (SelK2 or enoxaparin) or the TKA (for enoxaparin arm, if enoxaparin dosing is only done after TKA) up to the day of venography (Day 11 ± 2) or early study termination. Note that for patients randomized to receive SelK2, study drug can be dosed either the day prior to TKA (Day 1) or on the day of TKA (Day 2) as long as the dosing occurs at least 12 hours prior to but not longer than 24 hours prior to the start of the TKA surgery.

For those randomized to receive enoxaparin, patients will receive 40 mg enoxaparin administered via SC injection 12 hours after TKA surgery followed by daily SC injections of 40 mg enoxaparin for at least 9 additional days post-surgery (with the option of giving an additional 40 mg enoxaparin SC dose 12 hours prior to TKA surgery).

For those randomized to receive SelK2 and enoxaparin, patients will receive a single dose of 7.5 mg/kg SelK2 via IV administration at least 12 hours prior to but not longer than 24 hours prior to

the start of the TKA surgery and will receive 40 mg enoxaparin administered via SC injection 12 hours after TKA surgery followed by daily SC injections of 40 mg enoxaparin for at least 9 additional days post-surgery.

For all patients, the Treatment Phase will be completed on the day the venography is completed.

Patients will remain in the hospital for AT LEAST two overnights after TKA. During the Treatment Phase, efficacy, safety and PK/PD/Immunogenicity assessments will be completed for each patient.

3.4.3 Follow-Up Phase

After completion of the venography, each patient enters the Follow-Up Phase of the study which will last approximately 45 days. During this Phase, each patient will return for safety assessment on Day 21 and Day 57 (Final Study Visit). Patients will also be contacted on Day 29 and 43 by phone for assessment of any adverse events that have occurred since the last clinic visit.

3.4.4 Study Diagrams for SelK2 and Enoxaparin Arms

The following diagram depicts the Screening, Treatment, and Follow-Up Phases of the study for patients randomized to receive **SelK2**:

Screening Phase	Treatment Phase				Follow-Up Phase
Screening (Maximum 30 days prior to dosing)	Day 1 Baseline Assessments Randomization Single Dose of IV SelK2 7.5 mg/kg dosed 12 to 24 hours prior to TKA	Day 2 TKA	Days 3 -11 Assessment of Efficacy and Safety	Day 11 Venography	Follow-Up Assessments Through Day 57

The following diagram depicts the Screening, Treatment, and Follow-Up Phases of the study for patients randomized to receive **Enoxaparin**:

Screening Phase	Treatment Phase				Follow-Up Phase
Screening (Maximum 30 days prior to dosing)	Day 1 Baseline Assessments Randomization Optional Enoxaparin 40 mg SC at least 12 hours pre-TKA	Day 2 TKA Enoxaparin 40 mg SC 12 hours post-TKA	Days 3-11 Assessments of Efficacy and Safety Enoxaparin 40 mg SC, QD	Day 11 Venography	Follow-Up Assessments Through Day 57

IF Adaptive arm is activated:

The following diagram depicts the Screening, Treatment, and Follow-Up Safety Phases of the study for Patients Randomized to Receive **SelK2 and Enoxaparin**:

Screening Phase	Treatment Phase				Follow-Up Phase
Screening (Maximum 30 days prior to dosing)	Day 1 Baseline Assessments Randomization Single Dose of IV SelK2 7.5 mg/kg dosed 12 to 24 hours prior to TKA Optional Enoxaparin 40 mg SC at least 12 hours pre-TKA	Day 2 TKA Enoxaparin 40 mg SC 12 hours post-TKA	Days 3-11 Assessments of Efficacy and Safety Enoxaparin 40 mg SC, QD	Day 11 Venography	Follow-Up Assessments Through Day 57

3.5 Efficacy and Safety Assessments

Data for the assessment of efficacy will be collected during the Treatment and Follow-up Phases of this study. A venography will be performed on Study Day 11 (± 2 days) to assess the potential for the occurrence of an asymptomatic DVT. The venography as well as the reporting of any suspected venous thromboembolism will serve as the basis for efficacy assessments. Blood samples at various times throughout conduct of the study will also be drawn to evaluate hsCRP and D-dimer which are exploratory markers for inflammation and thrombosis.

Safety assessments will be performed throughout the study, at specified times prior to and following administration of study drug and active comparator during the Treatment and Follow-up Phases. Safety assessments will include: all adverse events including bleeding events or suspected bleeding events (e.g., suspicious reported AE), physical examinations, vital signs (blood pressure, pulse rate, respiratory rate, and body temperature), immunogenicity, clinical laboratory tests (Blood chemistry, Hematology panel, UA), additional laboratory evaluations (prothrombin time/international normalized ratio or PT/INR and activated partial thromboplastin time or aPTT), 12-lead electrocardiograms, and reported or observed AEs.

The Central Independent Adjudication Committee (CIAC) will evaluate in a blinded fashion all venograms, episodes of suspected VTE, and unexplained deaths and the outcome of the adjudication will be the basis for the final efficacy evaluations. The CIAC will also review all relevant data for each suspected bleeding event in a blinded fashion. Adjudicated data regarding efficacy and bleeding events will be used for both the interim and final analyses. The CIAC will also review any suspected arterial thrombotic events (e.g., myocardial infarction, ischemic stroke, etc.).

A formal study Steering and Safety Committee will consist of at least 3 clinicians (with experience and expertise in venous thrombosis) and one or more representatives from the Sponsor. The Steering and Safety Committee will be charged with reviewing in an unblinded fashion all accumulating safety and efficacy data to assure overall patient safety in this study. Further details about the composition and conduct of the Steering and Safety Committee and the data to be presented to this Committee can be found in Section 11.3. Additional details will also be provided in the Steering and Safety Committee Charter.

3.6 Endpoints

3.6.1 Primary Efficacy Endpoint

3.6.1.1 Incidence of Total Venous Thromboembolism

The incidence of total venous thromboembolism will consist of a composite of:

- Asymptomatic deep-vein thrombosis of the operated leg (detected by mandatory unilateral venography);
- confirmed symptomatic DVT of the leg(s);
- confirmed symptomatic pulmonary embolism; and
- unexplained death for which pulmonary embolism could not be ruled out.

A unilateral ascending venogram is to be performed on each study patient between Study Day 9 and Study Day 13 of study conduct (approximately 10 days after completion of TKA). The venogram will be obtained from the leg that underwent surgery. Multiple views of each venous segment will be obtained per instructions provided in the Manual for Venography and Event Reporting. The CIAC will review all venographic data in a blinded fashion for the adjudication of an endpoint event.

Study patients will be evaluated for signs and symptoms of DVT (e.g., swelling, localized pain, redness, heat, localized warmth) and PE (e.g., unexplained shortness of breath, coughing up blood, chest pain that gets worse with a deep breath, unexplained coughing) during the post-surgery in hospital/clinic period and at all visits occurring throughout the Treatment and Follow-up Phases of the study.

Every suspected episode of DVT or PE must be reported appropriately as an AE. The underlying clinical data from any patient with a suspected DVT or PE events will be presented to the CIAC and adjudication as a possible study endpoint.

3.6.2 Exploratory Efficacy Endpoints

3.6.2.1 Laboratory Markers of Inflamation and Thrombosis

Absolute changes from baseline in levels of high sensitivity C-reactive Protein (hsCRP) and D-dimer will be assessed.

3.6.3 Pharmacokinetic Assessments of SelK2

Pharmacokinetics will be assessed on all patients randomized to the SelK2 arm (and the adaptive arm of SelK2 and enoxaparin, if activated) by obtaining serum samples prior to receiving SelK2 dosing, throughout the Treatment Phase after SelK2 dosing, and during the Follow-Up Phase Visits.

Post-treamtent SelK2 concentrations for evaluable patients receiving SelK2 will be listed by study visit day and also summarized by descriptive statistics.

3.6.4 Pharmacodynamic Assessments of SelK2

Pharmacodynamics will be assessed on all patients randomized to the SelK2 arm (and the adaptive arm of SelK2 and enoxaparin, if activated) by obtaining serum samples prior to receiving SelK2 dosing, throughout the Treatment Phase of the study, and during the Follow-Up Phase Visits. In this assay, patient serum will be added to a P-selectin/PSGL-1 binding assay. The amount of active SelK2 in the serum will be inversely proportional to the degree of interaction between P-selectin and PSGL-1 as SelK2 binding inhibits this interaction. The PD of SelK2 will be reported as the percentage of P-selectin/PSGL-1 interaction that is inhibited by a given serum sample. Other markers of PD activity of SelK2 may be investigated.

The percent inhibition (%) will be listed by study visit day and also summarized by descriptive statistics.

3.6.5 Safety Endpoints

Safety parameters for this study include the following:

- Bleeding Events
- Other Adverse Events
- Clinical laboratory measurements
- Additional laboratory evaluations
- Physical examination and vital signs
- 12-lead ECGs
- Immunogenicity (anti-SelK2 antibodies) assessment
- Transfusion(s) with blood products
- Pregnancy test

Suspected bleeding events will be adjudicated in a blinded fashion for categorization as a:

1) Major Bleeding event (MB),
2) Clinically Relevant Non-Major Bleeding event (CRNMB),
3) Minor Bleeding, or
4) No Bleed.

The criteria for classification are specified in the CIAC charter and will include the classification for major bleeding in the surgical setting (8).

4.0 SELECTION OF STUDY POPULATION

A total of 190 patients will be enrolled, 95 patients in each of 2 arms of the study (Arm 1: 7.5 mg/kg SelK2, IV or Arm 2: 40 mg enoxaparin, SC, QD).

An additional adaptive arm of 95 patients may be added for the investigation of the combination of 7.5 mg/kg SelK2, IV and 40 mg enoxaparin, SC, QD.

4.1 Inclusion Criteria

Patients meeting all of the following criteria will be considered for admission to the study:

1. Males or females, between 18 and 80 years of age, inclusive;
2. Females must be non-pregnant and non-lactating, and either postmenopausal (>12 months since last menses) or using highly effective contraceptive measures as defined in the Clinical Trial Facilitation Group (CTFG) guidelines*;
3. Males, if engaged in sexual relations with a partner of child-bearing potential, must use highly effective contraceptive measures as defined in the Clinical Trial Facilitation Group (CTFG) guidelines*;
4. Planned to undergo elective, primary total unilateral TKA under general anesthesia; and
5. Able to comprehend and willing to give written informed consent.

4.2 Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. Body weight <50 kg at Screening;
2. Previous deep vein thrombosis (DVT) of the leg or pulmonary embolism (PE) within the past year;
3. Malignancy within 1 year, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated;
4. Myocardial infarction, transient ischemic attack or stroke within the last 6 months;
5. Patients at increased risk of bleeding because of history of increased bleeding tendency (i.e., history of bleeding diathesis) or any other condition that in the opinion of the Investigator increases risk of bleeding (e.g., recurrent gastrointestinal ulcer) or patients with a history of intracranial or intraocular bleeding;
6. Brain, spinal, or ophthalmologic surgery within the past 3 months;
7. Cockcroft-Gault calculated creatinine clearance <30 mL/min at Screening (central lab will calculate the Cockcroft-Gault value);
8. Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that, in the opinion of the PI, would render a patient unsuitable for inclusion:
    - ALT or AST >1.5x ULN
    - Total bilirubin >1.5x ULN

- Platelet count <150,000 or recent (over the last 3 months) history of thrombocytopenia (e.g. platelet count <150,000);

9. Positive test for human immunodeficiency virus (HIV; by history of having HIV antibodies), positive hepatitis B (hepatitis B surface antigen [HBsAg]) or hepatitis C (anti-hepatitis C antibody [Anti-HCV]) at Screening;
10. Uncontrolled hypertension as judged by the Investigator;
11. Clinically significant abnormal ECG at Screening, as judged by the Investigator;
12. Active infection;
13. Unable to undergo venography due to a known allergy to the contrast agent, anticipated poor venous access, impaired renal function, or any other reason identified and specified by the PI;
14. Hypersensitivity to enoxaparin or any contraindication listed in the local labeling of enoxaparin;
15. Any underlying condition (e.g., atrial fibrillation, mechanical heart valve, or recent pulmonary embolism) that may lead to the required concomitant use of anticoagulants/antiplatelet agents (e.g., warfarin, dabigatran, rivaroxaban, apixaban, clopidogrel) that may affect study outcome or any other drug influencing coagulation (except low dose aspirin (100 mg or less));
16. Anticipated use of intermittent pneumatic compression devices and/or electrical/mechanical muscle stimulators post TKA procedure;
17. Anticipated use of indwelling intrathecal or epidural catheters;
18. Participation in any other investigational study drug trial in which receipt of an investigational study drug occurred within 60 days prior to Day 1;
19. History of alcoholism or drug addiction within 1 year prior to Screening;
20. Any acute or chronic condition that, in the opinion of the Investigator, would limit the patient's ability to complete and/or participate in this clinical study; or
21. Unwillingness to comply with all study procedures including follow-up visits, as specified by this protocol, or unwillingness to cooperate fully with the Investigator.

* Birth control methods which are considered as highly effective are listed in the Clinical Trial Facilitation Group (CTFG) Guidance, Final Version – 2014-09-15.

One of these highly effective contraceptive methods must be used from the time of signing of the informed consent until 30 days after the Final Study Visit.

5.0 STUDY TREATMENTS

5.1 Study Drug Information

5.1.1 Description of Study Drug

[redacted]

SelK2 vials will be shipped in temperature-controlled shippers for delivery to site study personnel. A pharmacist or designated personnel will compound individual doses of active drug for study patients on a milligram per kilogram basis in a 100 mL infusion bag or bottle of a sterile 0.9% sodium chloride solution (0.9% Sodium Chloride Injection, USP) in accordance with the Pharmacy Manual. Study drug will be administered over 30 minutes by IV infusion. Patients will be monitored for 60 minutes following the infusion.

The active comparator is commercially available enoxaparin and will be provided by the Sponsor. Enoxaparin (enoxaparin sodium) will be provided as pre-filled syringes of 40 mg/0.4 mL (100 mg/mL concentration) of enoxaparin for SC injection. Sites may also use local supplies of commercially available enoxaparin if necessary.

5.1.2 Blinding, Packaging, and Labeling of Study Drug

This is a randomized and unblinded study, consequently no effort is required to blind study drug or active comparator from any of the study personnel at the clinical site. A pharmacist will be responsible for the compounding of individual doses of study drug (SelK2) for patients randomized to receive SelK2.

Each SelK2 vial is labeled in accordance with specific country regulatory requirements as well as with the study number, specific drug contents, and unique vial number.

Enoxaparin pre-filled syringes will be labeled in accordance with specific country regulatory requirements.

5.1.3 Randomization Methods and Procedures

Patients will be screened prior to randomization and assigned a Subject ID number by IRT. After patient's eligibility is confirmed, treatment assignment will be determined by a validated central randomization schedule using IRT (Interactive Response Technology). If a patient meets all of the inclusion criteria and none of the exclusion criteria, delegated and approved site personnel, trained on the use of the IRT, will randomize the patient. The IRT system will assign the patient a treatment group based on the next available slot in the randomization scheme. It is important to note that the randomization web entry should **only** be made after eligibility has been established. Prior to randomization, baseline efficacy and safety assessments will be taken.

Patients will be randomly placed into one of two treatment arms:

1) 7.5 mg/kg SelK2, IV or
2) 40 mg enoxaparin, SC, QD.

Patients will be randomized to these two treatment arms in a 1:1 ratio. Randomization will be stratified by site.

For patients randomized into the 7.5 mg/kg SelK2 arm, the IRT system will calculate the number of vials required based on the patient weight and will provide the user the appropriate vial numbers to use.

Changes in Randomization Procedure when Adaptive arm is activated and enrollment into the SelK2 only arm is discontinued:

When the adaptive arm is activated and the SelK2 only arm is closed, the central randomization process will allow for placing patients randomly into one of the below two treatment arms and randomization will continue to be stratified by site.

Patients will be randomly placed into one of two treatment arms:

1) 40 mg enoxaparin, SC, QD, or
2) 7.5 mg/kg SelK2, IV and 40 mg enoxaparin, SC, QD.

The randomization ratio will be altered to a 2:1 ratio (2 patients receiving 7.5 mg/kg SelK2 and enoxaparin to every 1 patient receiving Enoxaparin only) so that the total number of patients in each of the two remaining arms will be approximately equivalent at the end of the study. This modified randomization ratio will be controlled by the centralized IRT system.

5.1.4 Supply, Storage, Accountability, and Disposition of Study Drug

The pharmacist will inventory and acknowledge receipt of all shipments of study drug. All study drug must be kept in a locked area with access restricted to designated study personnel. The study drug must be stored in accordance with the package instructions. All storage records (i.e temperature logs) must be maintained. The pharmacist will also keep accurate records of the quantities of study drug dispensed and used by each patient. A monitor will ensure accountability of all study drug used. Refer to the Pharmacy Manual for further detailed instruction on study drug (both SelK2 and enoxaparin) storage and accountability.

At the conclusion of the study, after final drug reconciliation is completed by the monitor, all unused study drug can be destroyed at site (with appropriate documentation) or can be returned to a designee as instructed by Sponsor. IQVIA will assure that a final report of drug accountability is prepared and maintained by the Investigator.

Neither SelK2 nor enoxaparin will be provided to study participants after their participation in this study is completed. Neither SelK2 nor enoxaparin will be made available to any participants at the conclusion of this study.

5.2 Dosage Schedule

5.2.1 Dosing of SelK2

For those randomized to receive SelK2, patients will receive a single dose of 7.5 mg/kg SelK2 via IV administration at least 12 hours prior to but not longer than 24 hours prior to the start of the TKA surgery. SelK2 will be given as an approximately 100 mL IV infusion over approximately 30 minutes (± 15 minutes).

5.2.2 Dosing of Enoxaparin

For those randomized to receive enoxaparin, patients will receive 40 mg enoxaparin administered via SC injection 12 hours after TKA surgery followed by daily SC injections of 40 mg enoxaparin through and including Day 11 (± 2 days). Daily dosing of enoxaparin should continue until the venogram is completed. At the discretion of the PI, sites also have the option of giving an additional 40 mg enoxaparin SC dose 12 hours PRIOR to TKA surgery.

5.2.3 Adaptive Arm: Dosing of SelK2 and Enoxaparin

When the adaptive arm is activated, for those randomized to receive SelK2 and enoxaparin in combination, patients will receive a single dose of 7.5 mg/kg SelK2 via IV administration at least 12 hours prior to but not longer than 24 hours prior to the start of the TKA surgery. SelK2 will be given as an approximately 100 mL IV infusion over approximately 30 minutes (± 15 minutes). Additionally, patients will receive 40 mg enoxaparin administered via SC injection 12 hours after TKA surgery followed by daily SC injections of 40 mg enoxaparin through and including Day 11 (± 2 days).

5.3 Prior and Concomitant Medications

In general, medications consistent with the standard care of patients undergoing TKA (e.g., tranexamic acid, etc.) will be allowed during this study.

Except for the protocol prescribed SelK2 or enoxaparin, all efforts should be made to exclude the concomitant use of anticoagulants/antiplatelet agents (e.g., warfarin, dabigatran, rivaroxaban, apixaban, clopidogrel, phenprocoumon, acenocoumarol, edoxaban, prasugrel, ticagrelor, sulodexide, aspirin+dipyridamole, cilostazol, etc.) throughout the duration of the study, from Day 1 through Day 57 UNLESS medically necessary (i.e., patient experiences a VTE, myocardial infarction, etc.). Use of NSAIDs is discouraged and should only be used when unavoidable. NSAIDS should be used in the lowest dose and for the shortest period of time possible. Any concomitant use of aspirin should be avoided (except for low dose aspirin, 100 mg or less).

Any medication or non-pharmacological therapy (in addition to the study drug) that is taken by or administered to the patient at any point during the course of this study must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use. The collection of prior medications will include medications used within the past 6 months from the estimated Day 1 date.

Patients may not participate in any other interventional drug study for at least 60 days prior to starting this study (Study Day 1) and may not participate in any other interventional drug study throughout the study period.

6.0 STUDY PROCEDURES

6.1 Schedule of Events

The procedures and assessments to be performed during each phase of the study are outlined in the Study Schedule of Events (see Table 1).

Table 1. Study Procedures Schedule of Events for SELK2-00005

Study Procedures	Screening Phase	Treatment Phase						Day 21	Day 29 Phone Call	Day 43 Phone Call	Day 57 Final Study Visit/ Early Discontinuation Visit
		Day 1[a] (Randomization)	Day 2 (TKA)	Day 3	Day 4	Day 5 to Day 10	Day 11				
Visit Window (days)	30 days to 1 day prior to Randomization	N/A	N/A	N/A	N/A	± 2	± 2	± 2	± 2	± 2	± 2
Informed Consent	X										
Demographics	X										
Medical History	X	X[b]									
Physical Examination	X	X[c]			X[c]		X[c]	X[c]			X
12-Lead ECG	X				X						X
Vital Signs, Body Weight	X[d]	X[d]	X[e]		X		X	X			X
Chemistry, Hematology (CBC), and Urinalysis	X	X			X		X	X			X
PT/INR and aPTT	X	X			X		X	X			X
Samples for hsCRP, D-dimer analysis	X	X			X	X[f] (Day 6 Only)	X	X			X
HIV, Hepatitis B and C	X										
TKA Surgery			X								
Venography							X				
PK/PD Blood Samples (only SelK2 or adapt. arm)		X[g]	X[h]		X	X[f] (Day 6 Only)	X	X			X
Immunogenicity (only SelK2 or adapt. arm)		X[g]					X	X			X
Pregnancy Test	X[i]	X[i]									
Record Concomitant Medications and Transfusions	X	X	X	X	X	X	X	X	X	X	X
AE Assessment		X	X	X	X	X	X	X	X	X	X
IRT Randomization		X									
SelK2 Dosing (only SelK2 or adapt. arm)		X[j]									
Enoxaparin Dosing (only enoxaparin or adapt. arm)		X[k]	X[l]	X	X	X	X				

[a] All Day 1 assessments and activities need to be completed PRIOR to randomization.
[b] Interim medical history only to confirm no change in patient eligibility to be done prior to patient randomization.
[c] Abbreviated physical examination only (refer to Section 6.5.2.3).
[d] Body weight to be recorded only at Screening and on Day 1.
[e] Vital signs (temperature, respiration rate, blood pressure, and pulse) should be collected on Day 2 prior to TKA procedure.
[f] If patients remain in the hospital through Study Day 6, blood samples should be collected for PK/PD and Inflammatory and Thrombosis Markers of hsCRP and D-dimer.
[g] PK, PD and immunogenicity blood sampling to occur on Day 1 prior to SelK2 dosing.
[h] PK and PD blood sampling to occur on Day 2 prior to TKA approximately 12-24 hours after SelK2 dosing.
[i] For all females of child bearing potential, a serum pregnancy test will be conducted during Screening and, for women of child-bearing potential, a urine pregnancy test must be completed prior to randomization on Day 1. Both tests must be NEGATIVE prior to randomization on Day 1.
[j] SelK2 dosing should ONLY occur after randomization of patient to SelK2 arm (or those randomized to adaptive arm of SelK2 and enoxaparin).
[k] If PI/site plans to dose enoxaparin prior to TKA procedure, dosing can ONLY occur after randomization of patient to enoxaparin arm and should be dosed 12 hours prior to TKA surgery.
[l] Enoxaparin dosing on Day 2 should be administered SC 12 hours after TKA surgery.

N/A = Not Applicable; ECG=electrocardiogram; AE=adverse event; PD=pharmacodynamics; PK=pharmacokinetics; CBC=complete blood count; UA=urinalysis; PT/INR=prothrombin time/international normalized ratio; aPTT=activated partial thromboplastin time; HIV= human immunodeficiency virus; IRT= Interactive Response Technology; TKA= Total Knee Arthroplasty (Total Knee Replacement Surgery)

6.2 Screening Phase

This screening process will be conducted to confirm the patient's eligibility to participate in this study based on a review of all inclusion and exclusion criteria. The following procedures are to be performed within 30 days prior to Day 1 of the Treatment Phase (note, medical history can be used to confirm criteria as long as data was collected/verified within the 30-day screening phase):

1. Signed the Informed Consent;
2. Demographics including age, gender, race;
3. Medical history;
4. Complete physical examination (refer to section 6.5.2.3);
5. 12-lead ECG;
6. Vital signs including sitting blood pressure, pulse rate, respiratory rate, and temperature after sitting for 3-5 minutes, and body weight;
7. Collection of clinical laboratory samples (blood and urine) to be shipped to the central lab for evaluation of hematology, blood chemistry, coagulation parameters and urinalysis (See Section 6.5.2.2 for complete listing of analyses);
8. HIV antibody testing, Hepatitis B and C testing;
9. High Sensitivity C-reactive Protein (hsCRP) and D-dimer sample collection;
10. In female patients of child bearing potential perform serum pregnancy test; and
11. Record concomitant medications and transfusions.

Patients who meet all of the inclusion criteria and none of the exclusion criteria during the Screening Phase will be eligible for the study. At the Investigator's discretion, patients that are excluded from the study may be rescreened for study inclusion at a later date that is at least two weeks following the initial study exclusion. The primary reason for patient exclusions will be recorded in a screening log for patients who are not randomized.

No study-specific procedures will be performed prior to completion of informed consent by patient.

6.3 Treatment Phase

The schedule of assessments and procedures to be performed during the Treatment Phase are outlined below by Study Day and in the "Study Schedule of Events" (see Table 1).

6.3.1 Day 1

The following procedures are to be performed on Day 1. Day 1 can also serve as the day of Check-in to the hospital facility as an inpatient and serve as the beginning of the patient's stay at the hospital study site. (Day 1 activities could be conducted as an outpatient if assurance that patient will return to facility early on Day 2 for TKA).

IMPORTANT NOTE: All the listed assessments (1-8) are to be completed PRIOR to randomization.

1. Medical history (update any additional medical history or any changes in medical history that has occurred since the time of the Screening Visit);
2. Abbreviated physical examination (refer to section 6.5.2.3);
3. Vital signs including sitting blood pressure, pulse rate, respiratory rate, and temperature after sitting for 3-5 minutes, and body weight;
4. Collection of clinical laboratory samples (blood and urine) to be shipped to the central lab for evaluation of hematology, blood chemistry, coagulation parameters and urinalysis;
5. Collection of blood samples for hsCRP and D-dimer assessments;
6. Collection of blood samples for PK, PD, and immunogenicity assessments prior to study drug dosing;
7. In female patients of child-bearing potential, perform urine pregnancy test. The urine pregnancy test must be negative before randomization and dosing of study drug; and
8. Record any new or changes to concomitant medications and transfusions.

It is preferred that procedures are performed in following order: ECG and vital signs followed by blood draws.

If all of the inclusion criteria and none of the exclusion criteria (that are immediately evaluable) are met, patients can be enrolled in the study and the following activities can be completed on Day 1.

9. RANDOMIZATION of patient using IRT.
10. If patient is randomized to the SelK2 arm or SelK2 + enoxaparin arm, SelK2 dosing should be completed on Day 1 at least 12 hours but not more than 24 hours prior to beginning of TKA procedure. Patients MUST remain in the clinic for at least 1 hour after dosing with SelK2.
11. If patient is randomized to the enoxaparin arm or SelK2 + enoxaparin arm, site may choose to give a pre-surgery dose of enoxaparin 12 hours prior to TKA surgery.
12. Assessment of AE's.

6.3.2 Day 2

The following need to be completed prior to the start of the TKA procedure.

1. Vital signs including sitting blood pressure, pulse rate, respiratory rate, and temperature after sitting for 3-5 minutes;
2. Assessment of AEs; and
3. For patients in the SelK2 arm or SelK2 + enoxaparin arm, collection of blood samples for PK and PD assessments prior to start of TKA surgery but between 12 to 24 hours after SelK2 dosing.

Once these activities have been completed, patient can be prepared for the TKA procedure.

4. TKA procedure to be completed.

Once TKA is completed:

5. For patients randomized to the enoxaparin arm or SelK2 + enoxaparin arm, dosing of enoxaparin to occur 12 hours after TKA.
6. Recording of concomitant medications and transfusions; and
7. Assessment of AEs.

6.3.3 Day 3

Patients will remain in hospital facility during Day 3 and undergoing the following procedures.

1. For patients randomized to the enoxaparin arm or SelK2 + enoxaparin arm, dosing of enoxaparin;
2. Recording of concomitant medications and transfusions; and
3. Assessment of AEs.

6.3.4 Day 4

Patients will undergo the following procedures on Day 4.

1. Abbreviated physical examination;
2. 12-lead ECG;
3. Vital signs including sitting blood pressure, pulse rate, respiratory, and temperature after sitting for 3-5 minutes;
4. Collection of clinical laboratory samples (blood and urine) to be shipped to the central lab for evaluation of hematology, blood chemistry, coagulation parameters and urinalysis;
5. Collection of blood samples for hsCRP and D-dimer assessments;
6. For patients randomized to the SelK2 arm or SelK2 + enoxaparin arm, collection of blood samples for PK and PD assessments;
7. For patients randomized to the enoxaparin arm or SelK2 + enoxaparin arm, enoxaparin dosing;
8. Record any new concomitant medications and transfusions; and
9. Assessment of AEs.

Patients can be released from the hospital research site following completion of all assessments on Day 4.

6.3.5 Day 5 – Day 10

Patients can remain in the hospital site throughout Day 5 – Day 10 OR may be discharged from the hospital at any point during this time frame at the discretion of the site and their standard practices. Site personnel will be charged with collecting data on concomitant medications, transfusions, and assessment of AEs for each patient throughout this period.

For Days 5-10 regardless of whether or not patient is in hospital or discharged to home, patients will undergo the following procedures.

1. For patients randomized to the enoxaparin arm or SelK2 + enoxaparin arm, enoxaparin dosing.

For patient remaining in the hospital on Study Day 6, the following assessments should be done on Day 6 ONLY:

2. Collection of blood samples for hsCRP and D-dimer sample collection; and
3. For patients randomized to the SelK2 arm or SelK2 + enoxaparin arm, collection of blood samples for PK and PD assessments.

6.3.6 Day 11

Patients will undergo the following procedures on Day 11:

1. Abbreviated physical examination;
2. Vital signs including sitting blood pressure, pulse rate, respiratory, and temperature after sitting for 3-5 minutes;
3. Collection of clinical laboratory samples (blood and urine) to be shipped to the central lab for evaluation of hematology, blood chemistry, coagulation parameters and urinalysis;
4. Collection of blood samples for hsCRP and D-dimer assessments;
5. For patients randomized to the SelK2 arm or SelK2 + enoxaparin arm, collection of blood samples for PK, PD, and immunogenicity assessments;
6. For patients randomized to the enoxaparin arm or SelK2 + enoxaparin arm, enoxaparin dosing;
7. Venography;
8. Record concomitant medications and transfusions; and
9. Assessment of AEs.

Patients can be released from the hospital or clinic following completion of all assessments on Day 11.

6.4 Follow-Up Phase

The schedule of assessments and procedures to be performed during the Follow-up Phase are outlined below by Study Day and in the "Study Schedule of Events" (see Table 1).

6.4.1 Day 21

Patients will undergo the following procedures on Day 21.

1. Abbreviated physical examination;
2. Vital signs including sitting blood pressure, pulse rate, respiratory, and temperature after sitting for 3-5 minutes;
3. Collection of clinical laboratory samples (blood and urine) to be shipped to the central lab for evaluation of hematology, blood chemistry, coagulation parameters and urinalysis;
4. Collection of blood samples for hsCRP and D-dimer assessments;
5. For patients randomized to the SelK2 arm or SelK2 + enoxaparin arm, collection of blood samples for PK, PD, and immunogenicity assessments;
6. Record concomitant medications and transfusion; and
7. Assessment of AEs.

6.4.2 Day 29

Phone contact to assess the following:

1. Record concomitant medications and transfusions; and
2. Assessment of AEs.

6.4.3 Day 43

Phone contact to assess the following:

1. Record concomitant medications and transfusions; and
2. Assessment of AEs.

6.4.4 Day 57

Patients will undergo the following procedures on Day 57.

1. Complete physical examination;
2. 12-lead ECG;
3. Vital signs including sitting blood pressure, pulse rate, respiratory, and temperature after sitting for 3-5 minutes;
4. Collection of clinical laboratory samples (blood and urine) to be shipped to the central lab for evaluation of hematology, blood chemistry, coagulation parameters and urinalysis;
5. Collection of blood samples for hsCRP and D-dimer assessments;

6. For patients randomized to the SelK2 arm or SelK2 + enoxaparin arm, collection of blood samples for PK, PD, and immunogenicity assessments;
7. Record concomitant medications and transfusions; and
8. Assessment of AEs.

The completion of assessments listed above on Day 57 marks the completion of each patient in this study.

Patients should be reminded that they must remain on a highly effective contraceptive method until 30 days after their Final Study Visit.

6.4.5 Early Discontinuation Visit

IMPORTANT NOTE: For patients that are early terminating from the study, site personnel should make every effort to have patients undergo an Early Discontinuation Visit which has assessments identical to those done for the final safety visit on Day 57.

Patients will undergo the following procedures at their Early Discontinuation Visit

1. Complete physical examination;
2. 12-lead ECG;
3. Vital signs including sitting blood pressure, pulse rate, respiratory, and temperature after sitting for 3-5 minutes;
4. Collection of clinical laboratory samples (blood and urine) to be shipped to the central lab for evaluation of hematology, blood chemistry, coagulation parameters and urinalysis;
5. Collection of blood samples for hsCRP and D-dimer assessments;
6. For patients randomized to the SelK2 arm or SelK2 + enoxaparin arm, collection of blood samples for PK, PD, and immunogenicity assessments;
7. Record concomitant medications; and
8. Assessment of AEs.

6.5 Measurements and Assessments

Details of specific efficacy, safety, PK, and PD assessments are provided in this section. Additional details are provided in the Laboratory Manual.

6.5.1 Efficacy Assessments

6.5.1.1 Venography

A unilateral ascending venogram of the operated leg is to be performed for each study patient between Day 9 and Day 13 of the study, approximately 10 days after completion of TKA. The Manual for Venography and Event Reporting describes instructions for the venography and image acquisition. A venography will be evaluable when images with multiple views of all the deep veins of the leg can be evaluated (only exception is the deep femoral vein which sometimes difficult to visualize).

6.5.1.2 Suspected Symptomatic VTE

Patients will be evaluated for signs and symptoms of DVT (e.g., swelling, localized pain, redness, heat, localized warmth) and PE (e.g., unexplained shortness of breath, coughing up blood, chest pain that gets worse with a deep breath, unexplained coughing) during the post-surgery in hospital/clinic period and at all visits occurring throughout the Treatment and Follow-up Phases of the study. Patients with suspected DVT and or PE should undergo further diagnostic testing per hospital routine (e.g compression ultrasound for suspected DVT and spiral CT scan for patients with PE). Every suspected episode of DVT or PE must be reported appropriately as an AE and the underlying supportive data (e.g images and reports of diagnostic tests, hospital reports) will be submitted for adjudication by the CIAC. The Study Site Manual for Venography and Event Reporting provides instruction on the documentation, data collection, and reporting required for each suspected episode of DVT or PE.

If patients would have a PE or DVT confirmed by diagnostic testing during the Treatment Phase, the planned venography of the operated leg is not required.

If a patient would have an event that requires therapeutic anticoagulant treatment, the prophylactic dosing of enoxaparin will need to be discontinued. The anticoagulant treatment undertaken will be at the discretion of the treating physician and any question regarding SelK2 should be referred to the medical monitor by contacting the medical help line.

6.5.1.3 Laboratory Markers of Inflammation and Thrombosis

Blood sampling will be collected on Screening, Day 1, Day 4, Day 6 (optional), Day 11, Day 21, and Day 57 for assessment of hsCRP and D-dimer.

6.5.1.4 Pharmacokinetic and Pharmacodynamic Assessments of SelK2

Blood sampling will be performed to supply 2 mL of serum for PK evaluations and 2 mL of serum for PD evaluations in patients randomized to SelK2 arm or adaptive arm. Blood samples will be collected via an indwelling catheter and/or via direct venipuncture. Please note that since the PK and PD samples will generally be collected at the same time points, one tube will be used to collect both samples and then samples aliquoted accordingly.

Blood sampling will be collected on Day 1 (pre-dose SelK2), Day 2 (prior to TKA), Day 4, Day 6 (optional), Day 11, Day 21, and Day 57 for assessment of PK and PD.

The exact date and sampling time will be recorded on the appropriate eCRF page. Please refer to the Laboratory Manual for details of collection, storage, and shipping of samples.

The PK and PD assays will be performed at Cytovance Biologics, 840 Research Parkway, Suite 400, Oklahoma City, Oklahoma, USA 73104.

6.5.2 Safety Assessments

Safety assessments for this study include the following:

6.5.2.1 Adverse Events

Adverse events will be assessed by standard non-leading questions. All clinical AEs occurring from Randomization on Day 1 and up until the Day 57 visit whether observed by the investigator or reported by the patient will be assessed, documented, and reported in accordance with ICH GCP guidelines. Section 7.0 outlines the definitions, collection periods, criteria, and procedures for documenting, grading, and reporting AEs. A separate document that details AE eCRF completion guidelines for Investigators as well as training will be provided.

6.5.2.1.1 *Bleeding*

All suspected bleeding events are to be reported and additional examination will be done if deemed necessary by the investigator depending on the type of bleeding (e.g. hematology blood sample, endoscopy). If a patient has a hemorrhagic stroke both stroke and bleeding will be reviewed.

Narratives of bleeding events should be detailed and contain the following elements at the minimum:

- Location of the bleeding
- Size (in case of hematoma)
- Duration
- Provocation e.g. associated with any procedure
- Hemoglobin values prior and after bleeding if available
- Any transfusion or medication given

Other bleeding related parameters should be recorded during the trial:

- Hb level, HCT and red cell count changes during the treatment period
- Blood loss (peri-, post-operative) quantified by the routine method in each hospital
- Number of transfusions of packed red cells and transfused quantities until follow-up (e.g., 30 days after surgery; homologous and autologous transfusions need to be distinguished)

If a decrease in hemoglobin, blood loss or more transfusions are given than expected following TKA a suspect bleeding event needs to be reported and the narrative as specified above needs to be completed.

The data of all reported bleeding events or potential bleeding event must be submitted to the CIAC. The Study Site Manual for Venography and Event Reporting provides instruction for sites on the documentation, data collection, and reporting required for each suspected bleeding event.

Approach to Patients With Acute Bleeding

The following steps are recommended for patients with ongoing life-threatening bleeding (bleeding resulting in hemodynamic compromise requiring intervention or any intracranial hemorrhage):

- Withhold enoxaparin and all other anticoagulant/antiplatelets;
- Institute standard of care for life-threatening bleeding (large bore IV or central venous line, type and crossmatch blood, admit to the intensive care unit, provide hemodynamic and respiratory support);
- Administer antidotes if applicable (e.g., administer protamine if the patient had recently received heparin); and
- Administer packed red blood cells (or whole blood) as needed.

Use of prothrombin complex concentrates (PCCs), recombinant Factor VIIa, other factor procoagulants, or antifibrinolytics (depending upon the clinical situation and local availability) should be considered in consultation with a local available hematology expert. The SelK2 Medical Support Line (+32 495 54 74 51) can be contacted to discuss patient management (English language only).

6.5.2.1.2 *Stroke*

If a patient has a suspected stroke, the diagnostic work-up should be performed according to the hospital routine (it is expected that CT scans/MRI of the brain are done). Stroke will be reviewed by the CIAC to evaluate whether hemorrhagic stroke was present which will be considered as a major bleeding event.

6.5.2.1.3 *Death*

For patients who died, the adjudication committee will need to classify cause of death and will attribute death to PE if no other cause can be identified.

It is therefore crucial to provide a detailed description including the sequence of events preceding death (e.g. “patient gradually deteriorated and was found dead, or patient became suddenly short of breath and collapsed).

6.5.2.2 Clinical laboratory measurements

Blood (for hematology/CBC and clinical chemistry panel) and urine samples (for urinalysis) will be collected according to the Study Schedule of Events and analyzed at a central laboratory. All blood samples will be collected while patients are in a seated or supine position. Specific instructions for the collection, processing, and shipment of samples will be provided in the Laboratory Manual. Laboratory test results that are abnormal and considered clinically significant must be reported as AEs. Screening laboratory results must be available before randomization.

All of the major clinical laboratory assessments (including Clinical Chemistries, Hematology/CBC, complete Urinalysis (UA), coagulation parameters (PT/INR and aPTT) will be conducted at the central laboratory. In addition, at screening, samples for HIV (HIV antibody), Hepatitis B (HBsAg), Hepatitis C (Anti-HCV antibody) and serum pregnancy (women only) will be collected for analysis at central laboratory. All supplies for clinical laboratory sample collection will be provided in the form of kits from the central laboratory.

The samples for laboratory assays and the visits at which these samples will be collected are indicated in Table 1 (Study Procedures Schedule of Events).

Table 2 provides an exhaustive and complete listing of all the clinical laboratory assessments that will be included in this study.

Table 2. Listing of All Clinical Laboratory Assays Included in Clinical Chemistry, Hematology (CMC), Complete UA and Coagulation Parameters

Chemistry:	**Hematology (CBC):**	**Complete UA:**
Albumin	Hematocrit	pH and Specific Gravity
Alkaline Phosphatase	Hemoglobin	Glucose
Alanine Transaminase (ALT)	MCH	Protein
Aspartate Transaminase (AST)	MCHC	Blood
Blood urea nitrogen (BUN)	MCV	Ketones
Calcium	MPV	Reflexive Microscopic analysis (including RBCs and WBCs per high power field)
Chloride	Platelet count	
Bicarbonate/Carbon Dioxide (CO_2)	Red blood cell distribution width (RDW)	**Coagulation Parameters:**
Creatinine	Red blood cell (RBC) count	Prothrombin Time/International Normalized Ratio (PT/INR)
Direct Bilirubin	White blood cell (WBC) count	activated Partial Thromboplastin Time (aPTT)
Gamma glutamyl transferase (GGT)	White blood cell differential	
Glucose	(% & Absolute):	
Lactate Dehydrogenase (LDH)	Basophils	
Phosphorus	Eosinophils	
Potassium	Lymphocytes	
Sodium	Monocytes	
Total Bilirubin	Neutrophils	
Total Protein		
Uric acid		

6.5.2.3 Physical examination and vital signs

A complete physical examination and vital signs assessment will be performed at select study visits, as listed in the study schedule of events. A complete physical examination includes a review of the following systems: general appearance, head/eyes/ears/nose/throat (HEENT); neck; respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. At all other scheduled visits, an abbreviated physical examination including exam of general appearance, skin, respiratory, cardiovascular, and abdomen will be conducted.

Vital signs including sitting blood pressure (systolic and diastolic), pulse rate, respiratory rate, and temperature will be collected after sitting for 3-5 minutes. Body weight will also be measured.

After Screening, any clinically significant abnormal findings in physical exams or clinically significant vital signs should be reported as AEs.

6.5.2.4 12-lead ECGs

Standard, digital, 12-lead ECGs will be performed at all time points as indicated in the Study Schedule of Events. Additional 12-lead ECGs should be performed at any other time if clinically indicated. The performance of all ECGs must adhere to the following guidelines:

- All standard digital ECGs will be performed after the patient has been supine for at least 5 minutes.
- The ECG will be performed before any other procedures that may affect heart rate (e.g., blood draws).
- The ECG will be performed prior to dosing.
- When ECG time points coincide with PK blood sampling time points, the ECG must be performed before blood sampling so that any patient's response to the blood sampling does not cause a change in ECG interval durations.

A hard copy of the ECG will be printed at the site. To ensure safety of the patients, the Investigator or designee at the Investigator site will make comparisons to baseline measurements, which is defined as the most recent non-missing (scheduled or unscheduled) measurement collected prior to the initial administration of study drug. If a clinically significant finding is noted at any time on ECG, site will follow-up with a cardiology consult to verify initial ECG findings and further evaluate safety of patient.

See Study Procedures or Study Schedule of Events (Table 1) for assessment days.

6.5.2.5 Immunogenicity (anti-SelK2 antibodies) assessment

Serum samples will be collected according to the procedure described below:

Blood sampling will be performed to supply at least 1 mL of serum for immunogenicity assessments in patients randomized to the SelK2 arm or adaptive arm. Blood samples will be collected via an indwelling catheter and/or via direct venipuncture.

The exact date and sampling time will be recorded on the appropriate eCRF page. Please refer to the Laboratory Manual for details of collection, storage, and shipping of samples.

Immunogenicity evaluations will be performed at Cytovance Biologics, 840 Research Parkway, Suite 400, Oklahoma City, Oklahoma, USA 73104.

6.5.2.6 Urine Pregnancy test

A urine pregnancy tests will be performed on all woman of child-bearing potential at the site on the Day 1 prior to randomization. If the urine pregnancy test is positive and confirmed as correct, patient will not be allowed to be randomized into this clinical study.

7.0 ADVERSE EVENTS INCLUDING SPECIAL REPORTING REQUIREMENTS FOR POTENTIAL VTE AND BLEEDING ENDPOINT EVENTS

7.1 Procedures for Handling and Reporting Adverse Events

7.1.1 Adverse Event

An **adverse event** (AE) is any undesirable medical event affecting a patient during a clinical trial. An AE can therefore be defined as any sign, symptom, syndrome, or new illness that appears while a patient is participating in this clinical study (from Randomization to final study visit (either Day 57 Visit or Early Discontinuation Visit)) or, if present at baseline, worsens in a patient during the period of observation in the clinical study and that may impair the well-being of the patient. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be medically important (e.g., that require unscheduled diagnostic procedures, treatment measures, or result in withdrawal from the study). An AE may or may not have a causal relationship with the study drug. The period of observation for AEs is defined as from the point at which the patient is randomized into the study to the completion of the Follow-Up Phase assessments at Day 57 (or the Early Discontinuation Visit, if patient early discontinues).

An AE may be:

- A new illness;
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness;
- An effect of the study drug;
- Unrelated to participation in the clinical study; or
- A combination of one or more of these factors.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. However, the condition for which the surgery is required may be an AE. Planned surgical measures permitted by the study protocol and the condition(s) leading to these measures are not AEs.

Each AE is to be recorded only once on the "Adverse Event" eCRF page with *seriousness* and maximum *intensity* that occurred over the duration of the event. Each event also should be evaluated with respect to *causality* and *actions taken*. All AEs are to be monitored and recorded from the point of study Randomization through Day 57 (or earlier if patient discontinues from the study). For all AEs that require the patient to be discontinued from the study, the event(s) will be followed until final resolution or stabilization of the event(s). Note that unexpected SAEs should be reported as outlined in Section 7.1.2. Adverse events may be identified by spontaneous patient report or from standardized open-ended verbal probes.

The Investigator will classify and evaluate each AE as follows:

- Seriousness (see definition of SAEs in *Section 7.1.2*);
- Intensity ("Mild" [does not interfere with daily activities]; "Moderate" [interferes with daily activities]; "Severe" [prevents daily activities]);

- Relationship to study drug (Not Related [clearly not related to study drug], Unlikely Related [doubtfully related to the study drug], Possibly Related [may be related to study drug], Probably Related [likely related to study drug] or Definitely Related [clearly related to study drug]);
- Action taken (None, Required concomitant medication, Other [explain]); and
- Outcome (Recovered without sequelae, Resolved with sequelae, Ongoing, Unknown, Death).

Procedures Regarding Pregnancy

Pregnancy is considered an AE. Should a female patient become pregnant (must be confirmed by the serum pregnancy test) during the study, the medical monitor should be immediately notified, and the patient followed to term. Should the female partner of a male patient become pregnant during the male patient's enrollment in this study, the medical monitor should be immediately notified, and the male patient's partner should be followed to term, if consent is received by her.

7.1.2 Serious Adverse Event

A **serious adverse event (SAE)** is any AE that, at any dose of study drug or at any time during the period of observation:

- Results in death;
- Is immediately life-threatening;
- Requires or prolongs in-patient hospitalization;
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Involves congenital anomaly or malignancy;
- Is medically important; or
- Requires medical intervention to prevent permanent impairment or damage.

Hospital admissions and/or surgical operations planned before or during a study are not considered AEs/SAEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

"Medically important events" are events that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the patient or require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse. Such events should be documented and reported as SAEs via data entry into the appropriate eCRF (see Reporting Requirements below).

"Events requiring medical intervention to prevent permanent impairment or damage" are events where the Investigator believes that medical or surgical intervention is necessary to preclude permanent impairment of a body function or to prevent permanent damage to a body structure. As there is an overlap between the terms "medically important event" and "events requiring medical

intervention to prevent permanent impairment or damage", it is left to the discretion of the Investigator to select the more applicable of the two criteria when entering data on the eCRF about the SAE.

Reporting Requirements for Serious Adverse Events Are As Follows:

All serious adverse events (SAEs) that occur from the time of randomization through the end of the study (Day 57 Visit), whether or not considered related to study drug, must be reported via data entry into the appropriate eCRF or fax within 24 hours of occurrence.

Sites will be provided with phone and faxline numbers for each country, on the paper SAE back up form.

All SAEs should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

The Sponsor or its designated Contract Research Organization (CRO) will ensure that all regulatory reporting requirements are met.

7.1.3 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards

The sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations. The investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular deaths) involving his/her subjects to the IEC/IRB that approved the trial. In accordance with ICH GCP guidelines, the sponsor will inform the investigator of “findings that could adversely affect the safety of subjects, impact the conduct of the trial, or alter the IEC’s/IRB’s approval/favorable opinion to continue the trial.” In particular and in line with respective regulations, the sponsor will inform the investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (“suspected unexpected serious adverse reactions” [SUSARs]). The investigator should place copies of Safety reports in the Investigator Site File. National regulations with regard to Safety report notifications to investigators will be taken into account. When specifically required by regulations and guidelines, the sponsor will provide appropriate Safety reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting by the sponsor is not clearly defined by national or site-specific regulations, the investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety reports provided by the sponsor and of filing copies of all related correspondence in the Investigator Site File. For trials covered by the European Directive 2001/20/EC, the sponsor’s responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidances.

7.2 Adverse Events that are Potential Study Endpoint Events

Please note that AEs and SAEs that are listed below are being captured as events defined as endpoints for this clinical study (both efficacy and safety endpoints).

Symptomatic events that will be adjudicated include the following:

- Suspected symptomatic DVT
- Suspected symptomatic PE
- Suspected bleed
- Suspected stroke
- Death
- Suspected arterial thrombotic events (e.g., myocardial infarction, ischemic stroke, etc.)

Whenever the site becomes aware of one of these clinical events, it is crucial that the event is reported as soon as possible, preferably within 24 hours. These events must be reported following the rules as outlined for all adverse events in Section 7.1.

An appropriate event adjudication dossier will need to be submitted even if a suspected event is not confirmed by tests locally, for example if imaging did not confirm a new clinical event.

7.2.1 Reporting Requirements for AE's that are Potential Study Endpoints

The Study Site Manual for Venography and Event Reporting provides instruction for sites on the documentation, data collection, and reporting required for events considered (suspected) endpoints.

Typically for the above clinical events of suspected symptomatic DVT, suspected symptomatic PE, bleeding, stroke, or death, data will be collected in order to generate an adjudication dossier which will consist of eCRF data and supportive documentation which is assembled for review by the CIAC.

All suspected clinical outcomes must be reported as adverse events. Reporting a suspected outcome as an adverse event on the AE page in eCRF will automatically trigger an event specific form (refer also to eCRF completion guidelines). The eCRF triggered event forms contain a narrative section. In this narrative, a short clinical description should be provided: e.g. including symptom description and duration, eventually performed diagnostic tests or intervention with dates and description.

The supportive documentation (adjudication dossier) will depend on the type of clinical event and will typically consist of images and reports of the diagnostic tests done to explore the suspected clinical event, and other reports that could be relevant to the CIAC (e.g. medical records and/or hospital letters, discharge summaries, laboratory tests).

7.3 Monitoring of Subjects with Adverse Events

Any AE that occurs during the course of a clinical trial and is considered to be possibly related to the study drug must be monitored and followed up by the investigator until stabilization or until the outcome is known, unless the subject is documented as “lost to follow-up”. Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. The sponsor will actively follow-up and collect information on any AE that occurs during the course of a clinical trial, however while this activity will continue for any serious AEs until stabilization or until the outcome is known, it will be discontinued at the time of database lock for non-serious AEs.

7.4 Treatment Interruption or Discontinuation

If an adverse reaction occurs during the administration of study drug, the infusion rate may be slowed or interrupted and the appropriate supportive measures instituted at the discretion of the physician. If the infusion is slowed, the total infusion time should not exceed two hours. Monitor the patient for at least one hour following completion of the infusion for signs or symptoms of an infusion reaction.

As with all protein products, administration of study drug may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions. The infusion should be discontinued immediately if the patient experiences a serious infusion reaction such as signs of cardiovascular instability or respiratory compromise, and the appropriate supportive measures instituted. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms.

8.0 PATIENT WITHDRAWAL, REMOVAL OR SITE TERMINATION

8.1 Withdrawal or Removal of Patient From Study

Patients may withdraw from the study (withdraw consent) or be withdrawn by PI under the following circumstances:

- At their own request or at the request of their legally authorized representative;
- Patient is lost to follow-up;
- Investigator deems it necessary to stop study drug administration (e.g., for safety or for non-compliance to protocol); or
- At the specific request of the Sponsor.

In all cases, the reason for withdrawal must be recorded in the eCRF and in the patient's medical records. The patient must be evaluated to establish whether the reason was an AE, and, if so, this must be reported in accordance with the procedures outlined in Data Handling Procedures (see Section 9.0).

Even if the patient has decided to discontinue from the other study procedures, the Early Discontinuation Visit assessments should be performed approximately eight weeks after the patient's Day 1 (randomization) visit, if possible. In addition, those female patients required to use acceptable birth control during the study must be reminded that they should continue this form of birth control for a total of 10 weeks after receiving a dose of SelK2. The Investigator must make every effort to contact patients lost to follow-up on at least 2 occasions, including sending the patient a letter by certified mail (return receipt).

Occasionally patients may also withdraw consent to allow further data collection. Under such conditions, completion of the scheduled events, procedures, and assessments as specified in the protocol will not be possible. A record of the reason for discontinuation of data collection should be made on the appropriate eCRF page.

8.2 Termination of Study

The study may be terminated at any time for the following reasons: 1) Investigator/IRB/EC at a specific site after consultation with the Sponsor stops study for safety reasons; 2) Sponsor may also stop the study at one or more sites due to safety, site noncompliance, loss or lack of data quality, or project termination; 3) if the governing Regulatory Agency mandates study stop; or 4) for safety if recommended by the Steering Committee with Sponsor agreement. If the study is stopped at a site due to the action of the Investigator/IRB/EC, IQVIA and the Sponsor should be informed immediately. See Section 12.8 for further instructions on premature closure of the study.

9.0 DATA HANDLING PROCEDURES

9.1 Electronic Case Report Form Completion

Access to the eCRF will be granted to Investigator and/or delegated staff after completion of proper training. Data from source documents will be entered directly onto the eCRF by the Investigator or designated representative. The eCRF must be reviewed by the Investigator. The eCRF should be kept current to allow the clinical monitor to be able to review the patient's current status. Once the patient has completed the study and all data have been entered onto the eCRF, the eCRFs will be electronically signed by the Investigator.

9.2 Database Construction

Missing data and inconsistencies will be identified through an extensive computerized editing procedure. The accuracy of the clinical database will be verified through a series of reviews of data listings and other pertinent data processing reports. As a final quality control measure, the database will be proofread and the data listings will be reviewed to ensure that they are understandable, complete, and reliable.

10.0 STATISTICAL METHODS AND PLANNED ANALYSES

10.1 Sample Size and Power

Assuming that the rate of VTE for the active comparator (enoxaparin) arm of this study will be 25%, it is estimated that a sample size of 76 evaluable patients per arm should give the study 80% power of declaring non-inferiority between the SelK2 arm and the enoxaparin active comparator arm. This calculation uses a one-sided 90% CI with a non-inferiority margin of 15%. This calculation assumes that the underlying rate of VTE for the SelK2 and enoxaparin arms will be identical at 25% and with the non-inferiority margin set as at the midpoint between the expected active therapy response compared to an assumed placebo event rate in this patient population of 55%. Consequently, making the conservative estimate that up to 20% of randomized patients may not yield evaluable endpoint data, a total of 95 patients will be enrolled per arm to provide at least 76 endpoint evaluable patients per arm.

Sample Size Considerations for Adaptive Arm:

With the same assumptions as above the for active comparator (enoxaparin) arm of the study event rate, it is estimated that a sample size of 76 evaluable patients in a combination therapy arm of SelK2 and enoxaparin should give the study 80% power of declaring superiority between the SelK2 and enoxaparin arm and the enoxaparin active comparator arm for an estimated SelK2 and enoxaparin VTE event rate of 6% (an 19% difference between combination treatment effect and active comparator treatment effect). This calculation assumes a two-sided 0.1 alpha, a Pearson Chi-squared test, and a superiority comparison.

10.2 Analysis Populations

Assignment of patients to analysis populations will be done prior to clinical data lock for the study. The following populations will be defined: Intent-to-Treat (ITT), modified Intent-to-Treat (mITT), Per-Protocol (PP), and Safety.

Intent-to-Treat (ITT): All patients who are randomized. The ITT population will be analyzed by randomized treatment group.

Modified Intent-to-Treat (mITT): All patients in the ITT population who also have a successful venogram or symptomatic VTE event which allow for assessment of the primary efficacy outcome.

Per-Protocol (PP): All mITT patients who complete the study and have no major protocol violations that will impact the efficacy assessments.

Safety: All patients who received at least 1 dose of study drug. Safety population will be analyzed by actual treatment received.

10.3 Statistical Analysis

10.3.1 General Considerations

Descriptive summary statistics include mean, median, standard deviation, interquartile range, and range (minimum, maximum) for continuous variables, and counts and percentages for categorical

variables. Unless otherwise specified, continuous variables will be analyzed using two-sample t-test or Wilcoxon-Mann-Whitney test, whichever is appropriate; and categorical variables will be analyzed using chi-squared test or Fisher's exact test, whichever is appropriate.

SAS 9.3 or later will be used to perform statistical analysis. Unless otherwise specified, a two-sided p-value less than 0.05 will be considered statistically significant. No multiplicity adjustment will be made.

10.3.2 Background Characteristics

10.3.2.1 Patient Disposition

Both number and percentage of patients in the following categories will be summarized as appropriate:

- Randomized;
- Safety Population;
- ITT Population;
- mITT Population
- PP Population;
- Completed treatment visits; and
- Prematurely discontinued the study and the reasons for discontinuations.

Reasons for discontinuation and major protocol violations will be summarized by treatment groups for the ITT and mITT populations.

10.3.2.2 Demographics, Background, and Baseline Characteristics

Demographics, background (e.g., medical history), and baseline characteristics will be summarized. Protocol deviations/violations will be provided as a patient data listing only. Major protocol deviations/violations will be identified for analysis purposes.

The demographics and baseline characteristics summary will be presented for the ITT, mITT, PP, and safety populations to allow review of the characteristics of those included in the efficacy and safety analyses, which will be based on these analysis populations. Background (e.g., medical history) summary will be presented for the ITT population only.

10.3.2.3 Prior and Concomitant Medications

Medications used in this study will be coded by the World Health Organization Drug Dictionary (WHODD), and summarized as frequency tables for the preferred terms in 2 parts:

- Prior medication: any medication that started prior to the first dose of study drug, regardless of when it ended (collected for medications given up to 6 months prior to Day 1).

- Concomitant medication: medication received at or after dosing of study drug, or medication that was received prior to dosing with study drug and continued after dosing of study drug.

If medication start date is on the day of or after the first dose of study drug, then medication will be summarized as concomitant medication regardless of whether the medication end date is missing or not. If the medication end date is before the date of first dosing of study drug, then the medication will be summarized as prior medication regardless of whether the medication start date is missing or not. Note that medication that started prior to first dosing of study drug and continued after dosing will be summarized as prior medication and separately as concomitant medication. Both prior and concomitant medications will be based on the ITT population. For medications with partial start dates, missing month will be imputed with January and missing day will be imputed with 1. For medications with partial stop dates, missing month will be imputed with December and missing day will be imputed with the last day of the month.

10.3.3 Efficacy Analyses

For all efficacy analyses, the main analysis will be based on the mITT population. Both primary and secondary endpoint analyses will also be performed on the PP population; these analyses will be supportive only. Comparisons will be made between the SelK2 treated patients SelK2 and enoxaparin treated patients, and the enoxaparin group. The difference of the total VTE rate during the Treatment Phase (from time of randomization up until the day of completion of venogram) between the SelK2, SelK2 and enoxaparin, and enoxaparin treatment groups will be estimated. The lower 1-sided 90% CI of the difference will be calculated and non-inferiority will be concluded if the upper limit of the 90% CI is $\leq$ 15%. The same analysis will be completed on the PP population.

The following secondary analyses will be performed on the mITT and PP populations:

- Comparison of the rates of the individual components of the primary efficacy outcome between the SelK2, SelK2 and enoxaparin, and enoxaparin treatment groups through Treatment Period.

- Conduct primary efficacy analysis of the total VTE rate between the SelK2 treatment, SelK2 and enoxaparin treatment, and enoxaparin treatment with the inclusion of events through Study Day 57.

- Complete comparison of the rates of the indivudal components of the primary efficacy outcome between the SelK2, SelK2 and enoxaparin, and enoxaparing treatment groups with the inclusion of events through Study Day 57.

Absolute changes from baseline in hsCRP and D-dimer will be summarized by treatment group at each post-baseline visit. Change from baseline in each parameter will be analyzed and compared between treatment groups using a mixed linear model with repeated measures (MMRM).

10.3.4 Pharmacokinetics and Pharmacodynamics

Serum pre- and post-treatment SelK2 concentrations for evaluable patients receiving SelK2 will be listed by dose, day and patient and also summarized by descriptive statistics.

Potential relationships between selected pharmacodynamics and plasma exposure measures may be explored, where deemed appropriate.

10.4 Safety Analysis

All treatment-emergent AEs and SAEs will be summarized by treatment using the MedDRA coding system, by system organ class, preferred term, relationship to Study Drug and severity (See Section 10.4.1).

Incidence of bleeding events (as adjudicated by the CIAC) including the following will be tabulated by treatment:

1) Major Bleeding event (MB),
2) Clinically Relevant Non-Major Bleeding event (CRNMB),
3) Minor Bleeding event, or
4) Combination of MB and CRNMB

Additionally, the overall safety profile of study drug will be assessed in terms of the following safety and tolerability endpoints:

- Incidence of treatment-emergent adverse events (TEAEs),
- Clinical laboratory values (hematology, serum chemistries, urinalysis, and coagulation parameters),
- ECGs,
- Vital signs.

These safety endpoint measures will be tabulated by treatment arm and study visit (and timepoint, where appropriate) and may also be presented as change and percent change from baseline, as appropriate.

Safety analysis will be based on the set of data associated with the period from randomization through the final Follow-Up Phase visit (Day 57). All Safety analyses will be performed on the safety population. Descriptive analysis of the above safety parameters will be performed.

10.4.1 Adverse Events

For analyses purposes, adverse events will be classified as pre-treatment emergent, treatment emergent, or post-treatment emergent. Adverse events which start (or increase in severity) during the period from the signing of informed consent up to, but not including, the first dose of study drug will be considered pre-treatment emergent. Adverse events which start (or increase in severity) during the period from the first dose of study drug through completion of the final Follow-up Visit (Day 57) will be considered treatment emergent. Adverse events which start (or increase in severity) after the completion of the Follow-Up Visit will be considered post-treatment emergent. For AEs with partial start dates, missing month will be imputed with January and missing day will be imputed with 1.

Adverse event summary tables will be presented for AEs only and will include the following:

- All treatment-emergent adverse events (TEAEs) or by severity or by relationship,
- Related (defined as possibly related or related) TEAEs,
- TEAEs leading to treatment discontinuation,
- Serious TEAEs, and
- Frequently reported TEAEs.

Summaries will be presented by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term using frequency counts and percentages (i.e., number and percentage of patients with an event as well as total number of events). Patients with multiple occurrences of the same adverse event or a continuing adverse event will be counted once; only the maximum severity level of this AE will be presented in the severity summaries; and only the worst/highest relationship level of this AE will be presented in the relationship summaries. A separate table will summarize all TEAEs when each of them is considered unique, hereafter referred as adverse event count table. In addition, a listing containing individual patient adverse event data for all deaths and other serious and significant adverse events will be provided, separately. All adverse events including pre- and post-treatment adverse events will be presented in individual patient data listings.

Narratives of deaths, serious and significant adverse events, including early withdrawals due to adverse events, will also be provided.

10.4.2 Clinical Laboratory Assessments

For results reported by the central laboratory, continuous hematology and chemistry results will be summarized in SI units by treatment group at each scheduled time point. Visits summarized will include baseline and post baseline visits, including early termination and Follow-Up. Changes from baseline will also be summarized at each time point. The number and percentage of patients with shift changes from baseline based on the laboratory normal ranges will be tabulated by treatment group and scheduled time point.

Urinalysis results and serum pregnancy test results will be listed in individual patient data listings only. In addition, a listing containing individual patient hematology, chemistry, and coagulation values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

10.4.3 Electrocardiogram

Standard digital ECG assessments will be conducted at baseline and post-baseline visits. A summary of raw values and change from baseline values will be provided by treatment group at each scheduled time point for the following standard digital ECG measurements: PR, QT, and QT corrected for HR (QTc) intervals (Fridericia correction [QTcF = QT/RR0.33] and Bazett correction [QTcB = QT/RR0.50]), QRS duration, and HR. The number and percentage of patients with shift changes from baseline based on the overall ECG evaluation will be tabulated by treatment group and visit. In addition, the number and percentage of patients will be tabulated by maximum on-treatment value of QT/QTc intervals, categorized as ≤450 msec, >450 msec and ≤480 msec, >480

msec and ≤500 msec, and >500 msec, as well as maximum on-treatment change from baseline value of QT/QTc intervals, categorized as ≤30 msec, >30 msec and ≤60 msec, and >60 msec.

10.4.4 Vital Signs

The following vital signs will be summarized by treatment group at each scheduled time point: systolic and diastolic blood pressure (mmHg), body temperature (°C), heart rate (beats per minute [bpm]), respiratory rate (breaths per minute), and body weight (kg). Absolute changes from baseline will also be summarized.

10.4.5 Physical Examination

Findings of the physical examination will be presented as a data listing only.

10.5 Steering and Safety Committee Data Reviews and Interim Analyses

A formal study Steering and Safety Committee will consist of at least 3 clinicians (with experience and expertise in venous thrombosis). The Steering and Safety Committee will be charged with reviewing in an unblinded fashion all accumulating safety and efficacy data to assure overall patient safety in this study.

The following efficacy and safety data will be provided to the Steering and Safety Committee by treatment group, and where appropriate by study visit day and time:

- Overall VTE event rate (as adjudicated);
- Individual component event rate (individual components of the composite VTE event rate);
- Incidence of bleeding events (as adjudicated) including the following will be tabulated by treatment:
    1) Major Bleeding event (MB),
    2) Clinically Relevant Non-Major Bleeding event (CRNMB),
    3) Minor Bleeding even, or
    4) Combination of MB and CRNMB
- Incidence of AEs (including SAEs) ;
- Clinical laboratory values (hematology, serum chemistries, urinalysis, and coagulation parameters);
- ECGs; and
- Vital signs.

The Steering and Safety Committee will use all of the above accumulating data to assess the safety of continuing each aspect of this study.

Interim Analyses to support decision on whether or not to recommend activation of Adaptive Arm:

The Steering and Safety Committee is also charged with making recommendations to the Sponsor with regards to the activation of the adaptive arm that investigates the efficacy and safety of SelK2 use in combination with enoxaparin. At certain enrollment milestones, the Steering and Safety Committee will be presented with interim analysis tables which will include VTE event rates by treatment group with 80% confidence intervals and the calculated risk difference (the difference

between the cumulative incidence in the SelK2 arm to that of the cumulative incidence the enoxaparin arm) with 80% confidence intervals. The conditional powers for demonstrating non-inferiority at the end of the trial based upon accumulated data at interim may also be computed. These interim analyses will be part of the data set used by the Committee as they determine whether or not to recommend activation of adaptive arm. This adaptive arm may be initiated if the Steering and Safety Committee determines that preliminary data suggests the potential for an additive effect in VTE reduction and that the combination does not pose an additional safety risk.

11.0 STUDY OPERATONS

The overall clinical operations of the study will be managed by IQVIA, a Contract Research Organization (CRO), Itreas, an Academic Research Organization (ARO), and the Sponsor. Other formal study committees include: Steering and Safety Committee and the Central Independent Adjudication Committee (CIAC).

11.1 IQVIA - Contract Research Organization

Day to day operations of this study will be conducted by IQVIA (4820 Emperor Blvd, Durham, NC 27703 USA), which will ensure the study is conducted with the highest ethical, legal, and regulatory standards, according to Good Clinical Practice/ICH Guidelines. All site selection, initiation, periodic monitoring, and closeout activities will be handled by this organization.

11.2 Itreas - Academic Research Organization

Itreas (Honthorststraat 2A, 1071 DD Amsterdam, the Netherlands) will perform medical monitoring responsibilities for this study. This will include the review of all accumulating safety and efficacy data for this study. Itreas will also be responsible for overseeing the Medical Monitor Telephone Support Line. The Medical Monitor Telephone Support Line is a 24 hour-a-day/7 days-a-week support telephone line for this study that can be contacted by any site personnel when study specific questions or issues arise. In addition, Itreas will coordinate and manage the collection and adjudication of all study endpoint events. This will include coordinating data collection from the clinical sites, assembling of adjudication dossiers for each event, and managing the adjudication process as completed by the CIAC.

11.3 Steering and Safety Committee

The Steering and Safety Committee is responsible for the overall clinical and scientific oversight of this trial. The scope of its responsibilities include the ongoing review of accumulating safety and efficacy data in an unblinded fashion. These reviews will include review of (a) venography results, (b) symptomatic venous thromboembolism [DVT/PE], bleeding and death, (c) all other SAEs, (d) clinical laboratory values, ECGs, and vital sign assessments to assure overall patient safety in this study. The Steering and Safety Committee will review all efficacy and safety data in an unblinded fashion and provide guidance and recommendations to the Sponsor regarding any needed study modifications. This Committee will also make recommendations to the Sponsor regarding activation of the adaptive arm of the study when sufficient data has accumulated to make such recommendation.

Further details about the presentation of data to the Steering and Safety Committee will be contained in the Steering and Safety Committee Charter.

After completing their unblinded reviews of accumulating safety and efficacy data, the Steering and Safety Committee will make a global assessment of safety and risk and will be empowered to make the following study recommendations:

1) Continue the study without modification;

2) Continue the study contingent upon making recommended study design changes through amendment of the protocol;

3) Continue study but pause enrollment, pending resolution of a specified issue;

4) Terminate the study.

11.4 Central Independent Adjudication Committee

The scheduled unilateral venography, all episodes of suspected venous thrombosis [DVT/PE], bleedings, stroke and deaths will be reviewed by the CIAC in a blinded fashion, i.e., not aware of the treatment assignment. The procedures followed by the CIAC are described in the adjudication charter. Adjudication results will be the basis for the final endpoint and safety analyses.

12.0 ETHICAL ISSUES, LEGAL ASPECTS, AND ADMINISTRATIVE ISSUES

12.1 Good Clinical Practice

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigator abide by good clinical practice (GCP). Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki.

12.2 Delegation of Investigator Responsibilities

The Investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. The Investigator should maintain a list of Sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

12.3 Patient Information and Informed Consent

Before being admitted to the clinical research study, the patient must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him. An informed consent document that includes both information about the study and the consent form will be prepared and given to the patient. The ICF must contain the 20 elements of informed consent described in ICH E6, Section 4.8. The document must be in a language understandable to the patient and must specify who informed the patient.

After reading the informed consent document, the patient must give consent in writing. The patient's consent must be confirmed at the time of consent by the personally dated signature of the person conducting the informed consent discussions. A copy of the signed consent document must be given to the patient or the patient's legally authorized representative. “Legally authorized representative” means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient’s participation in the procedure(s) involved in the research. The original signed consent document will be retained by the Investigator. The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

The Investigator should inform the patient’s primary physician about the patient’s participation in the trial if the patient has a primary physician and if the patient agrees to the primary physician being informed.

For patients who require a parent or legal guardian’s permission to participate, two consent documents will be used. One for obtaining the parent or guardian’s permission and one, which outlines the study in simplified language, for obtaining the assent of the patient. The process will be the same as outlined above.

12.4 Confidentiality

Patient names will not be supplied to the Sponsor. Only the randomization number and patient initials will be recorded in the eCRF, and if the patient name appears on any other document (e.g., pathologist report), it must be redacted before a copy of the document is supplied to the Sponsor.

Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be told that representatives of the Sponsor, EC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection law. The Investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

12.5 Protocol Amendments

Neither the Investigators nor the Sponsor will alter this study protocol without obtaining the written agreement of the other. Substantive changes in the protocol include changes that affect the safety of patients or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of patients treated, or the patient selection criteria must be prepared as a protocol amendment by the Sponsor and implemented only upon joint approval of the Sponsor and the Investigator. Once the study has started, amendments should be made only in exceptional cases. The changes then become part of the study protocol.

12.6 Approval of the Study Protocol and Amendments

Before the start of the study, the study protocol, informed consent documents, and any other appropriate documents will be submitted to the Ethics Committee (EC) / Institutional Review Board (IRB) with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought.

Study drug can only be supplied to the Investigator after documentation on **all** ethical and legal requirements for starting the study has been received by the Sponsor. This documentation must also include a list of the members of the EC/IRB and their occupation and qualifications. If the EC/IRB will not disclose the names of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. The EC/IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the EC/IRB should preferably mention the study title, study code, study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member.

Before the first patient is enrolled in the study, all ethical and legal requirements must be met.

The EC/IRB must be informed of all subsequent protocol amendments, in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent documents should also be revised.

The Investigator must keep a record of all communication with the EC/IRB and, if applicable, between a coordinating Investigator and the EC/IRB. This also applies to any communication between the Investigator (or coordinating Investigator, if applicable) and the authorities.

12.7 Ongoing Information for Ethics Committee / Institutional Review Board

If required by legislation or the EC/IRB, the Investigator must submit to the EC/IRB:

- Information on unexpected SAEs as soon as possible; and

- Periodic reports on the progress of the study.

12.8 Premature Closure of the Study

The Sponsor or the Investigator has the right to close this study at any time. As far as possible, this should occur after mutual consultation. The EC/IRB must be informed, if required by legislation.

Should the study be closed prematurely, all study materials (completed, partially completed and blank eCRFs, study drug, etc.) must be returned to the Sponsor or its designate, as if the study had been completed.

12.9 Record Retention

The following records must be retained by the Investigator for 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:

- Signed informed consent documents for all patients;
- Patient identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the EC/IRB;
- Composition of the EC/IRB;
- Record of all communications between the Investigator and Sponsor (or CRO);
- List of Subinvestigators and other appropriately qualified persons to whom the Investigator has delegated significant trial-related duties, together with their roles in the study and their signatures;
- Copies of CRFs and of documentation of corrections for all patients;
- Drug accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (patient records, hospital records, laboratory records, etc.); and
- All other documents as listed in Section 8 of the ICH (step 4) consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

However, because of international regulatory requirements, the Sponsor may request retention for a longer period of time. The Investigator must therefore obtain approval in writing from the Sponsor prior to destruction of any records. Normally, these records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, he must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

12.10 Liability and Insurance

The Sponsor provides insurance for study patients to make available compensation in case of study-related injury. Liability and insurance provisions for this study are given in the Investigator's contract.

12.11 Study Monitoring and Auditing

Monitoring and auditing procedures compliant with ICH GCP guidelines will be followed. On-site checking of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

12.11.1 Study monitoring

The study will be monitored by a CRO. Monitoring will be done by on-site visits from a clinical monitor who will review the eCRFs and source documents. By frequent communications (email, letter, telephone, and/or fax) and site visits, the clinical monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

12.11.2 Source data verification and on-site audits

Regulatory authorities, the EC/IRB and/or the Sponsor's clinical quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audits or inspections. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Study CRO will be completing on-site source data verification (monitoring) of selected data fields entered into eCRF.

13.0 DOCUMENTATION AND USE OF STUDY FINDINGS

13.1 Documentation of Study Findings

An electronic CRF (eCRF) will be completed for each patient. All protocol-required information collected during the study must be recorded by the Investigator, or designated representative, in the source documents and transcribed to the eCRF. If the Investigator authorizes other personnel to make changes to the eCRF, the names, positions, signatures, and initials of these persons must be supplied to the Sponsor. Any changes to the eCRF are to be verified by the authorized individual.

The eCRF must be reviewed and signed by the Investigator or by a designated Sub-Investigator. The site will receive a CD with all the site's eCRFs after database is locked.

13.2 Use of Study Findings

All information concerning the product as well as any matter concerning the operation of Tetherex Pharmaceuticals, such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have been provided by Tetherex Pharmaceuticals and are unpublished, are confidential and must remain the sole property of Tetherex Pharmaceuticals. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from Tetherex Pharmaceuticals is obtained. Tetherex Pharmaceuticals has full ownership of the eCRFs completed as part of the study.

By signing the study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registrations, publications, and information for medical and pharmaceutical professionals by Tetherex Pharmaceuticals. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

The Investigator may not publish or present any information on this study without the express written approval of Tetherex Pharmaceuticals. Additionally, Tetherex Pharmaceuticals may, for any reason, withhold approval for publication or presentation.

14.0 REFERENCES

1. Quinlan, D. J., Eikelboom, J. W., Dahl, O. E., Eriksson, B. I., Sidhu, P. S., and Hirsh, J. (2007) Association between asymptomatic deep vein thrombosis detected by venography and symptomatic venous thromboembolism in patients undergoing elective hip or knee surgery. *J Thromb Haemost* **5**, 1438-1443
2. Ramacciotti, E., Myers, D. D., Jr., Wrobleski, S. K., Deatrick, K. B., Londy, F. J., Rectenwald, J. E., Henke, P. K., Schaub, R. G., and Wakefield, T. W. (2010) P-selectin/ PSGL-1 inhibitors versus enoxaparin in the resolution of venous thrombosis: a meta-analysis. *Thromb Res* **125**, e138-142
3. Diaz, J. A., Wrobleski, S. K., Alvarado, C. M., Hawley, A. E., Doornbos, N. K., Lester, P. A., Lowe, S. E., Gabriel, J. E., Roelofs, K. J., Henke, P. K., Schaub, R. G., Wakefield, T. W., and Myers, D. D., Jr. (2015) P-selectin inhibition therapeutically promotes thrombus resolution and prevents vein wall fibrosis better than enoxaparin and an inhibitor to von Willebrand factor. *Arterioscler Thromb Vasc Biol* **35**, 829-837
4. Yeh, C. H., Gross, P. L., and Weitz, J. I. (2014) Evolving use of new oral anticoagulants for treatment of venous thromboembolism. *Blood* **124**, 1020-1028
5. Crowther, M. A., and Warkentin, T. E. (2008) Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. *Blood* **111**, 4871-4879
6. Lobo, E. D., Hansen, R. J., and Balthasar, J. P. (2004) Antibody pharmacokinetics and pharmacodynamics. *J Pharm Sci* **93**, 2645-2668
7. Dall'Acqua, W. F., Woods, R. M., Ward, E. S., Palaszynski, S. R., Patel, N. K., Brewah, Y. A., Wu, H., Kiener, P. A., and Langermann, S. (2002) Increasing the affinity of a human IgG1 for the neonatal Fc receptor: biological consequences. *J Immunol* **169**, 5171-5180
8. Schulman, S., Angeras, U., Bergqvist, D., Eriksson, B., Lassen, M. R., Fisher, W., Subcommittee on Control of Anticoagulation of the, S., Standardization Committee of the International Society on, T., and Haemostasis. (2010) Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost* **8**, 202-204

Listing of Significant Protocol Modifications

Section	Description of Changes
Synopsis, Study Design Section and Section 3.1 Basic Design Characteristics	Synopsis Revised Text Previously: Adaptive Design: The Steering and Safety Committee will review the accumulating efficacy and safety data and based upon the safety and efficacy profile of SelK2 may decide to modify enrollment, potentially adding a third study arm testing 7.5 mg/kg SelK2 given in addition to enoxaparin (40 mg, SC, QD). Now: Adaptive Design: The Steering and Safety Committee and Sponsor will review the accumulating efficacy and safety data at planned intervals, and based upon the safety and efficacy profile of SelK2 may decide to modify enrollment by adding a third study arm testing 7.5 mg/kg SelK2 given in addition to enoxaparin (40 mg, SC, QD) and removal of the SelK2 only arm. The two remaining arms will enroll patients in a 2:1 ratio with two patients receiving SelK2 and Enoxaparin for every one patient receiving Enoxaparin only at doses shown below: 1.) 7.5 mg/kg SelK2 (IV, single-dose) and 40 mg Enoxaparin, SC, QD 2.) Active Comparator (40 mg Enoxaparin, SC, QD) Section 3.1 Text Added: Upon activation of the adaptive arm and discontinuation of the SelK2 only arm of the study, during the Treatment Phase each patient will receive either: 1. A single 7.5 mg/kg dose of SelK2 (7.5 mg/kg, IV, single dose) and Enoxaparin (40 mg SC, QD for up to 10 ± 2 days) 2. Active Comparator Enoxaparin (40 mg, SC, QD for up to 10 ± 2 days)
Synopsis, Duration of Treatment and Section 3.4.2 Treatment Phase	Synopsis Add Text: Upon activation of the adaptive arm and discontinuation of the SelK2 only arm of the study, during the Treatment Phase each patient will receive either: 1) A single 7.5 mg/kg dose of SelK2 administered intravenously 12 to 24 hours prior to the initiation of the TKA surgery AND 40 mg dose of enoxaparin administered SC 12 hours after TKA surgery followed by daily injections of 40 mg enoxaparin, SC for at least 9 additional days post-surgery and up to the day of the planned venography, or 2) 40 mg dose of enoxaparin (active comparator) administered SC 12 hours after TKA surgery followed by daily injections of 40 mg enoxaparin, SC for at least 9 additional days post-surgery and up to the day of the planned venography (with the option of giving an additional 40 mg enoxaparin, SC dose 12 hours prior to TKA surgery).

Section	Description of Changes
	Section 3.4.2 Text Added: For those randomize to receive SelK2 and enoxaparin, patients will receive a single dose of 7.5 mg/kg SelK2 via IV administration at least 12 hours prior to but not longer than 24 hours prior to the start of the TKA surgery and will receive 40 mg enoxaparin administered via SC injection 12 hours after TKA surgery followed by daily SC injections of 40 mg enoxaparin for at least 9 additional days post-surgery.
Section 5.1.3 Randomization Methods and Procedures	Section 5.1.3 Text Change: Previously: *Changes in Randomization Procedure if Adaptive arm is activated:* If the adaptive arm is activated, a third arm will be added to the study and the central randomization process will then allow for placing patients randomly into one of three treatment arms. Randomization will continue to be stratified by site. Patients will be randomly placed into one of three treatment arms: 1) 7.5 mg/kg SelK2, IV or 2) 40 mg enoxaparin, SC, QD, or 3) 7.5 mg/kg SelK2, IV and 40 mg enoxaparin, SC, QD. The activation of the adaptive arm, if it occurs, is planned at a time in the study conduct when a significant portion (ranging between 33%-50%) of patients will have already been randomized to one of the two previously opened arms (7.5 mg/kg SelK2, IV or 40 mg enoxaparin, SC, QD). Consequently, the randomization ratio will be altered after addition of the third arm to allow for the total number of patients to be enrolled in each of the three arms to be equivalent. This modified randomization ratio will be controlled by the centralized IRT system. Now: *Changes in Randomization Procedure when Adaptive arm is activated and enrollment into the SelK2 only arm is discontinued:* When the adaptive arm is activated and the SeLK2 only arm is closed, the central randomization process will allow for placing patients randomly into one of the below two treatment arms and randomization will continue to be stratified by site. Patients will be randomly placed into one of two treatment arms: 1) 40 mg enoxaparin, SC, QD, or 2) 7.5 mg/kg SelK2, IV and 40 mg enoxaparin, SC, QD. The randomization ratio will be altered to a 2:1 ratio (2 patients receiving 7.5 mg/kg SelK2 and enoxaparin to every 1 patient receiving Enoxaparin only) so that the total number of patients in each of the two remaining arms will be approximately equivalent at the end of the study. This modified randomization ratio will be controlled by the centralized IRT system.

Section	Description of Changes
Synopsis, Safety Section and Section 3.5 Safety and Efficacy Assessments and Section 6.0 Study Procedures	Remove “oral” as the only manner in which to measure body temperature
Synopsis Safety Section And Section 3.5 Safety and efficacy Assessments And Section 6.0 Study Procedures	Add “of child bearing potential” to description of women for which serum pregnancy test should be completed
Section 5.2.3. Adaptive Arm: Dosing of SelK2 and Enoxaparin	Section 5.2.3 Delete: At the discretion of the PI, sites also have the option of giving an additional 40 mg enoxaparin SC dose 12 hours PRIOR to TKA surgery. If both SelK2 and enoxaparin dosing are planned for prior to the start of the TKA surgery, SelK2 should be given prior to the enoxaparin dosing.
Synopsis, Statistical Methods and Section 10.3.3 Efficacy Analysis	Clarify that all primary and secondary analyses will compare SelK2 only, SelK2 and Enoxaparin, and Enoxaparin only arms