Clinical Study Protocol

A PHASE 2, MULTICENTER, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROL STUDY OF REGN9933, A FACTOR XI MONOCLONAL ANTIBODY, FOR PREVENTION OF VENOUS THROMBOEMBOLISM AFTER ELECTIVE, UNILATERAL, TOTAL KNEE ARTHROPLASTY

Compound:	REGN9933
Clinical Phase:	2
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Medical /Study Director:	[redacted]

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AMENDMENT HISTORY

Overall Rationale for Amendment 1

The purpose of this non-substantial amendment is to incorporate responses to Health Authority (HA) feedback. The table below provides a summary of changes made to the protocol and the affected sections:

Description of Change	**Brief Rationale**	**Section # and Name**
Updated text for consistency with the newly added Section 8.8.2 Permitted Medications. Added text to clarify that the use of anti-coagulants for VTE prophylaxis is prohibited for subjects randomized to REGN9933 and to provide a rationale for this.	In response to HA feedback, updated text to clarify the permitted and prohibited medications.	Section 3.2.1 Rationale for Study Design
Added the italicized wording to the sentence: "If NovoSeven or another Factor VIIa formulation *is available* and selected for use at the discretion of the treating physician, the literature has commonly reported NovoSeven doses of 15 µg/kg to 30 µg/kg administered as an IV bolus in FXI-deficient patients"	In response to HA feedback, added text to clarify that the availability of Factor VII at study sites is not mandated by the protocol	Section 8.2.2 Treatment of Bleeding Events

Description of Change	Brief Rationale	Section # and Name
Created Section 8.8.2 Permitted Medications Text in Section 8.8.1 Prohibited Medications and Procedure reorganized for clarity and for consistency with the newly created Section 8.8.2 Permitted Medications Added statement that the use of standard-of-care medications not listed as prohibited will be allowed. Added text to clarify that, for subjects assigned to either the enoxaparin or apixaban treatment arm, continued VTE prophylaxis (after completion of protocol-defined treatment, ie through the day of venography [(or day 12, whichever is earlier]) is permitted, if deemed necessary by the site investigator based on local guidelines and/or clinical judgment. Moved the information on permitted vaccines from Section 8.8.1 Prohibited Medications and Procedures to Section 8.8.2 Permitted Medication	In response to HA feedback, added new Permitted Medications section, and updated text to clarify the permitted and prohibited medications.	Section 8.8.1 Prohibited Medications and Procedures Section 8.8.2 Permitted Medications
Reference to Regulation EU No 536/2014 added	In response to HA feedback, updated sections to refer to Regulation EU No 536/2014 for: • expedited reporting of SUSARs in the EU • quality control and quality assurance requirements in the EU	Section 10.4: Notifying Health Authorities, Institutional Review Board /Ethics Committee, and Investigators Section 12: Quality Control and Quality Assurance

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AC	Adjudication Committee
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ASA	Acetylsalicylic acid
BID	Twice daily
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CSR	Clinical study report
CT	Computed tomography
CTFG	Clinical Trial Facilitation Group
CRNM	Clinically relevant non-major
DOAC	Direct oral anticoagulants
DVT	Deep venous thrombosis
EU	European Union
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
FAS	Full analysis set
FBR	Future biomedical research
FSH	Follicle stimulating hormone
FXI	Factor XI
FXIIa	Factor XIIa
FXI:C	Factor XI functional activity
GCP	Good Clinical Practice
HIT	Heparin-induced thrombocytopenia
HIV	Human immunodeficiency virus
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee

IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Hemostasis
INR	International normalized ration
IV	Intravenous
IVRS/IWRS	Interactive voice response system/ interactive web response system
LMWH	Low molecular weight heparin
MDRD	Modification of Diet in Renal Disease
mITT	Modified intent to treat
MR	Magnetic resonance
NOAEL	No observed adverse effect level
OR	Odds ratio
OR_{RA}	the odds ratio of confirmed VTE in participants administered REGN9933 as compared to that of apixaban
OR_{RE}	the odds ratio of confirmed VTE in participants administered REGN9933 as compared to that of enoxaparin
PD	Pharmacodynamics
PE	Pulmonary embolism
PK	Pharmacokinetic
PO	Orally
PRO	Patient reported outcomes
PT	Prothrombin time
RBQM	Risk-Based Quality Monitoring
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SC	Subcutaneous
SmPC	Summary of product characteristics
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TGA	Thrombin generation assay
TKA	Total knee arthroplasty
ULN	Upper level of normal
VTE	Venous thromboembolism
WBC	White blood cell
WOCBP	Women of child-bearing potential

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 2, Multicenter, Randomized, Open-Label, Active-Control Study of REGN9933, a Factor XI Monoclonal Antibody, for Prevention of Venous Thromboembolism after Elective, Unilateral, Total Knee Arthroplasty
Site Location(s)	Up to approximately 25 sites globally
Principal Investigator	Principal investigator(s) will be identified and documented in the trial master file
Objective(s)	**Primary Objective** The primary objective of the study is to evaluate the efficacy of REGN9933 for the prevention of venous thromboembolism (VTE) after unilateral total knee arthroplasty (TKA), compared to enoxaparin **Secondary Objectives** The secondary objectives of the study are: • To evaluate the bleeding risk (ie, major and clinically relevant non-major [CRNM] bleeding) of REGN9933 after unilateral TKA through time of venography, compared to enoxaparin • To assess overall safety and tolerability of REGN9933 in participants undergoing TKA • To evaluate the efficacy of REGN9933 in prevention of clinically relevant VTE, compared to enoxaparin • To evaluate the efficacy of REGN9933 in prevention of DVT detected by venography, compared to enoxaparin • To evaluate the pharmacokinetics (PK) of REGN9933 after single intravenous (IV) administration • To assess pharmacodynamic (PD) effects of REGN9933 on intrinsic and extrinsic coagulation pathways (ie, aPTT, PT) • To assess immunogenicity following a single dose of REGN9933 over time • To compare the efficacy of enoxaparin and apixaban in prevention of VTE after unilateral TKA
Study Design	This is a phase 2 multicenter, multinational, randomized, open label, active-control study of a single dose of IV REGN9933 for prevention of VTE in participants undergoing an elective, unilateral, TKA.

	Participants who are at least 50 years of age and undergoing elective, unilateral TKA will be randomized after surgery to one of 3 treatment arms—REGN9933, enoxaparin, apixaban—in a ratio of 1:1:1, in a parallel manner. Participants will be stratified based on study site and age (<70 vs ≥70 years of age). Approximately 120 participants will be enrolled in each arm, for a total of up to approximately 360 participants in the study. Participants will be randomized after completion of surgery to receive a single dose of REGN9933 300 mg IV, enoxaparin 40 mg subcutaneous (SC) daily through the time of venography, or apixaban 2.5 mg orally twice daily through the time of venography. Discharge from the hospital will be determined by the site investigator based on individual participant recovery and local practice. Participants will undergo unilateral venography of the operated leg performed on day 10 (±2 days). While in the hospital after surgery and at subsequent study visits, participants will be assessed for signs and symptoms of symptomatic DVT and pulmonary embolism (PE). If DVT or PE is suspected, objective confirmatory testing should be obtained. Participants will be followed until the end-of-study visit on day 75. Assessments will include scheduled venography; adverse event (AE) monitoring; physical exams; clinical laboratory testing (hematology, chemistry, coagulation, and urinalysis); electrocardiogram (ECG); PK, PD, and biomarker sampling.
Study Duration	The duration of the study for a participant is approximately 75 days, excluding the screening period.
End of Study Definition	The definition for end of study (trial) is the date of global last participant's last visit, or the date of withdrawal from the study, or lost to follow-up (ie, the study participant can no longer be contacted by the investigator).
Population	
Sample Size:	Up to approximately 360 participants will be enrolled in the study
Target Population:	The study population will consist of adults who are at least 50 years of age and undergoing an elective, unilateral TKA.
Treatment(s)	
Study Drug	REGN9933
Dose/Route/Schedule:	300 mg IV, single dose administered as 0.5-hour infusion

Reference Drug	Enoxaparin
Dose/Route/Schedule:	40 mg SC, daily through the time of venography (or day 12, whichever is earlier)
Reference Drug	Apixaban
Route/Schedule:	2.5 mg orally, twice daily through the time of venography (or day 12, whichever is earlier)

Endpoint(s)

Primary: The primary endpoint is the incidence of confirmed, adjudicated VTE through day 12 (REGN9933 vs enoxaparin).

Secondary: The secondary endpoints are:

- Incidence of major bleeding and clinically relevant non-major bleeding through time of venography (or day 12, whichever is earlier).
- Incidence of treatment-emergent adverse events (TEAE) through the end of study
- Incidence of major VTE through day 12 (REGN9933 vs enoxaparin)
- Incidence of DVT as measured by venography of the operated leg on day 10 ± 2 days (REGN9933 vs enoxaparin)
- Concentrations of REGN9933 in serum through end of study
- Change in activated partial thromboplastin time from baseline through end of study
- Change in prothrombin time from baseline through end of study
- Incidence and titer of anti-drug antibodies (ADA) to REGN9933 through end of study
- Incidence of confirmed, adjudicated VTE through day 12 (enoxaparin vs apixaban)

Procedures and Assessments

Efficacy Procedures: Venography of the operated leg will be performed on day 10 (±2 days). If DVT or PE is suspected at any point during the study, objective confirmatory testing should be carried out.

Safety Procedures: Safety assessments will include body weight, height, monitoring of vital signs, physical examination, ECG, assessment for bleeding, laboratory testing, and the monitoring and reporting of AEs.

	Blood samples will be collected for drug concentration, total Factor XI concentration, ADA, and exploratory biomarker and research measurements and assessments.
Statistical Plan	**Statistical Hypothesis**: The clinical hypothesis comparing the efficacy of REGN9933 to enoxaparin will be assessed through a Bayesian estimation framework. Bayesian posterior probabilities will be reported to estimate the incidence of confirmed VTE for participants treated with REGN9933 and enoxaparin, as well as the odds ratio (OR) of confirmed VTE in participants administered REGN9933 as compared to that of enoxaparin (OR_{RE}). The statistical hypothesis $OR_{RE} < 1$. **Justification of Sample Size**: Up to a total of approximately 360 participants will be randomized in a 1:1:1 allocation ratio to REGN9933, apixaban or enoxaparin. Each arm will have an approximate number of 120 participants. The sample size was determined using the following assumptions: • The event rate of VTE for REGN9933 was assumed to be 13% and was set to be 22.4% for enoxaparin • The prior distribution of the treatment difference was assumed to be log(OR)~N(0,0.843), which was expressed as the log(OR). The prior distribution follows a normal distribution centered around no treatment difference and with a variance such that extreme treatment differences are expected to be unlikely, ie the probability that OR is between 0.25 and 4 is 90%. Using these assumptions, and for the purpose of choosing a sample size, the following quantities were simulated: • The probability of any beneficial effect of REGN9933 over enoxaparin, ie, the posterior distribution of the odds ratio comparing REGN9933 to enoxaparin of confirmed VTE. A beneficial effect is where $OR_{RE} < 1$, and thus the study will estimate $P(OR_{RE} < 1 \mid data)$. • In 75% of the simulated trials, in studies where the $P(OR_{RE} < 1 \mid data) > 0.95$, the sample size was 120 participants or less. Therefore, a sample size of 120 subjects per group was chosen. **Statistical Methods**: The clinical objectives will be estimated using the posterior distribution of OR_{RE}. For comparison of REGN9933 vs enoxaparin, different posterior probabilities will be provided, such as P(OR<0.5, 0.9, 1.0, 1.1, 1.2 etc|data).

The entire posterior density function for the treatment effect (OR_{RE} and the OR of confirmed VTE in participants administered REGN9933 as compared to that of apixaban) will be computed, along with the cumulative posterior distribution, which quantifies evidence for all possible treatment effects. A prior for treatment difference log(OR)~N(0,0.843) will be used. Bayesian summary statistics including two-sided 95% Highest Density Interval, posterior mean, and median will be reported. Summary statistics based on the raw data including the number of participants reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum will be reported.

The Kaplan-Meier plot for cumulative incidence of confirmed VTE over time will be provided by treatment groups. Subjects dropped out before the venogram or with missing venograms are considered as censored.

Safety will be assessed by clinical and statistical review of all relevant parameters, including vital signs, physical examinations, ECGs, laboratory evaluations, and AEs.

1. INTRODUCTION

Anticoagulants are medications used to treat and prevent venous and arterial thrombotic and embolic events by interfering with components of the coagulation cascade. The major complication of anticoagulants in clinical usage (such as warfarin, heparins, direct oral anticoagulants [DOAC]) is bleeding, since these drugs not only reduce thrombus formation, but also impair hemostasis. Furthermore, the bleeding liability of current anticoagulants has been associated with their blockade of the extrinsic and common pathways of the coagulation system (Harter, 2015). A major goal in the development of novel anticoagulants is to minimize bleeding risk while maintaining efficacy; targeting the intrinsic pathway is hypothesized to preserve normal hemostatic mechanisms and therefore carry less bleeding risk.

Inhibition of Factor XI (FXI), a component of the intrinsic pathway, has emerged as a promising approach for effective anticoagulation (ie, prevention of thrombus) with minimal effect on hemostasis. Patients with FXI deficiency (Hemophilia C) have well documented reductions in thromboembolic disease with a relatively mild bleeding phenotype and no other obvious deleterious effects. In addition, a retrospective study including more than 10,000 patients observed that FXI activity <50% of normal was associated with a decreased incidence of cardiovascular events (eg, stroke, transient ischemic attack, and myocardial infarction) and a reduced risk of venous thromboembolism (Preis, 2017). Preclinical studies using either genetic or pharmacologic reduction of FXI support the anti-thrombotic activity of FXI inhibition (Wang, 2005) (Yau, 2014). Finally, several therapeutics aimed at reducing FXI levels and/or activity have demonstrated promising antithrombotic activity, without evidence of increased bleeding risk, as compared to enoxaparin, in clinical studies (Büller, 2015) (Verhamme, 2021) (Weitz, 2020) (Weitz, 2021). In summary, blockade of FXI activity may prevent thromboembolic events without increasing bleeding risk (Hsu, 2021).

Factor XI can be activated by Factor XIIa (FXIIa). Factor XIIa activation is the initial step in the intrinsic pathway of coagulation and can be triggered by contact with negatively charged molecules, including polyphosphates from bacteria or platelets, free nucleic acids, misfolded proteins, or nonbiological surfaces (Al-Horani, 2018). [redacted]

REGN9933 is a monoclonal antibody which binds to FXI [redacted]. Thus, REGN9933 may prevent pathologic thrombosis due to activation of the intrinsic pathway of coagulation, while potentially maintaining hemostatic mechanisms distal to FXIIa activation of FXI.

REGN9933 is being evaluated in an ongoing randomized, double-blind, placebo-controlled phase 1 clinical study in healthy volunteers (study R9933-HV-2107). As of 01 Aug 2022, this ongoing study has randomized and dosed 40 subjects across 5 intravenous (IV) cohorts. Each cohort contained 8 subjects (6 randomized to REGN9933 and 2 randomized to placebo) at the following REGN9933 dose levels: 3 mg, 10 mg, 30 mg, 100 mg, and 300 mg. As of 01 Aug 2022, no adverse events (AEs) considered by the investigator to be related to study drug, no severe AEs, and no serious adverse events (SAEs) or clinically significant bleeding have reported in this ongoing study.

A dose-dependent prolongation of the activated partial thromboplastin time (aPTT) was observed across these 5 cohorts with an aPTT mean change from baseline of approximately 2.5-fold at the 100 mg IV and 300 mg IV dose levels (see Section 3.2.2). No dose-dependent trends have been observed in the prothrombin time (PT), and no safety concerns have been identified to date.

Refer to the Investigator's Brochure (IB) for additional background information on REGN9933 and the development program to date.

This study is assessing the occurrence of VTE after TKA, which is a commonly used clinical setting to demonstrate proof-of-concept of the antithrombotic effects of novel anticoagulants. Venous thromboembolism includes deep venous thrombosis (DVT) of the lower extremities and pulmonary embolism (PE). Patients undergoing TKA are at high risk of developing VTE in the post-operative period, due to local tissue trauma, immobility, and inflammation. Venous thrombosis (most of which is asymptomatic) is extremely common in the days following TKA, with rates reported on placebo of >50% (Agnelli, 2004). Even with approved therapies that reduce the rates of symptomatic VTE, the incidence of asymptomatic VTE is substantial (Verhamme, 2021) (Warwick, 2010) (Weitz, 2020), allowing for detection of relative efficacy compared to approved agents. Thrombosis may be reliably detected with protocol venography performed 8 to 12 days after surgery. Many anticoagulants have established proof-of-concept using this model, and subsequently shown clinical efficacy in other clinical settings, such as prevention of stroke in patients with atrial fibrillation. As a result, use of this model allows for benchmarking of REGN9933 against many other comparable drugs, and can also potentially serve as a proof-of-concept to help inform further development in other clinical settings.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to evaluate the efficacy of REGN9933 for the prevention of VTE after unilateral TKA, compared to enoxaparin.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the bleeding risk (ie, major and clinically relevant non-major [CRNM] bleeding) of REGN9933 after unilateral TKA through time of venography, compared to enoxaparin
- To assess overall safety and tolerability of REGN9933 in participants undergoing TKA
- To evaluate the efficacy of REGN9933 in prevention of clinically relevant VTE, compared to enoxaparin
- To evaluate the efficacy of REGN9933 in prevention of DVT detected by venography, compared to enoxaparin
- To evaluate the pharmacokinetics (PK) of REGN9933 after single IV administration
- To assess PD effects of REGN9933 on intrinsic and extrinsic coagulation pathways (ie, aPTT, PT)
- To assess immunogenicity following a single dose of REGN9933 over time
- To compare the efficacy of enoxaparin and apixaban in prevention of VTE after unilateral TKA

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- Explore the efficacy of REGN9933 in prevention of VTE after unilateral TKA through the end of study, compared to enoxaparin and apixaban
- Explore the efficacy of REGN9933 in prevention of symptomatic, clinical thrombosis, compared to enoxaparin and apixaban
- Explore the efficacy of REGN9933 in prevention of DVT detected by venography, compared to apixaban
- Explore the extent of DVT burden on venography in participants receiving REGN9933 compared to enoxaparin and apixaban
- Explore the bleeding risk (ie, major bleeds and CRNM) of REGN9933 after unilateral TKA through end of study compared to enoxaparin and apixaban
- Explore the occurrence of minor bleeding compared to enoxaparin and apixaban

- Explore biomarkers related to FXI inhibition by REGN9933
- Develop a molecular understanding of venous thromboembolism, and related diseases
- Explore relationships between PK, biomarkers of anticoagulant activity, and efficacy
- To study REGN9933 mechanism of action the coagulation cascade, VTE, and related diseases
- Explore whether potential differences in participant efficacy and safety are associated with genotype and gene expression and further study FXI and coagulation-related diseases, using optional whole blood DNA and RNA collected from consented subjects

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

REGN9933 will reduce the incidence of VTE after elective unilateral TKA as compared to enoxaparin.

3.2. Rationale

3.2.1. Rationale for Study Design

The population for this study is adults undergoing elective, unilateral TKA. Participants less than 50 years of age are excluded, due to a significantly lower incidence of symptomatic VTE relative to older participants (Lee, 2015). Weight greater than 130 kg is exclusionary to limit the variability in exposure and PD effect of the fixed dosing regimen of the antibody. Since venography will provide most of the events that make up the primary endpoint, those with or at high risk of contrast allergy will be excluded. Participants with contraindications to enoxaparin, such as a history of heparin-induced thrombocytopenia (HIT), or apixaban will not be enrolled. Several risk factors for abnormal bleeding or clotting are also exclusionary. Finally, women of child-bearing potential (WOCBP) are excluded, since the risk of bleeding in the setting of FXI inhibition in this subpopulation is not yet characterized; further, the age cutoff of > 50 years of age already precludes nearly all WOCBP.

Participants will be stratified by two factors: age (< 70 vs ≥ 70 years of age), based on the higher incidence of DVT in the ≥ 70 years age group (Lee, 2015); and site, to account for local variation in surgical and anesthesia practices.

Several medications are approved in the countries in which the trial will be conducted for the prevention of VTE after TKA; therefore, a placebo-treated group would not be appropriate. Enoxaparin, a low molecular weight heparin (LMWH), is approved for the prevention of VTE after orthopedic surgery. In European Union (EU) countries, the approved dose is 40 mg SC once daily (Inhixa [Summary of Product Characteristics], 2021). Refer to Section 3.3.2.1 for discussion on enoxaparin dosing in Canada. Dosing will start 12 to 24 hours after surgery in this study, per the label. The duration of treatment is a minimum of 7 to 14 days per the label, and this can be extended up to 35 days (Inhixa [Summary of Product Characteristics], 2021) (Lovenox [Product Monograph], 2021), although the benefit of longer duration treatment is more pronounced after total hip replacement relative to TKA (Comp, 2001) (Eikelboom, 2001). In this study, study drug treatment will occur through the time of venography (or day 12, whichever is earlier). Several recent studies using this paradigm have utilized enoxaparin as an active comparator (Büller, 2015) (Verhamme, 2021) (Weitz, 2020) (Weitz, 2021), allowing for benchmarking of results from this study to other agents in development.

Apixaban, a DOAC, is approved for the prevention of VTE after orthopedic surgery (Eliquis [Summary of Product Characteristics], 2021), and has also shown efficacy in prevention of VTE after TKA. In these studies, the regimen of apixaban evaluated was 2.5 mg twice daily (BID), initiated 12 to 24 hours after surgery, and continued for 10 to 14 days after surgery (Lassen, 2010) (Lassen, 2009). Apixaban serves as a calibrator in this study; a difference between apixaban and enoxaparin is expected and will be descriptively evaluated as a positive control. In addition, it will be useful to gain an early understanding of how REGN9933 compares to apixaban.

Timing of initiation of anticoagulants for prophylaxis of thrombosis following total knee replacement is a balance between safety and efficacy. Dosing closer to the time of surgery may confer additional efficacy but at the expense of increased bleeding risk. Apixaban and enoxaparin will be started at 12 to 24 hours post-operatively, consistent with labeled dosing regimens and REGN9933 will also be dosed at 12 to 24 hours post-surgery, to allow a direct comparison. Dosing of FXI inhibitors in this time range, as well as pre-operatively, has been shown to well-tolerated in published trials of FXI inhibitors (Büller, 2015) (Verhamme, 2021) (Weitz, 2020).

Regarding duration of treatment, for subjects assigned to study drug treatment with enoxaparin or apixaban, subsequent VTE prophylaxis (beyond day 12 or day of venography) may be determined by the site investigator as guided by local standard of care (see Permitted Medications, Section 8.8.2). However, for subjects assigned to REGN9933, use of anti-coagulants for VTE prophylaxis is prohibited, because REGN9933 elevates aPTT through at least day 35 (see Figure 1).

Treatment is administered in an open-label manner because enoxaparin is packaged in pre-filled syringes, making blinding operationally challenging. In addition, performing the study in a blinded manner would require most (two thirds) of the participants to take placebo injections, which would have increased participant burden. To mitigate bias, participants will be randomized to treatment assignment. To further mitigate bias in outcome assessment, adjudication of outcomes related to VTE and bleeding (ie, results of venograms and any confirmatory study for symptomatic VTE; categorization of bleeding events) will be performed by a centralized adjudication committee (AC) that is blinded to treatment assignment (Section 6.3.3).

The primary efficacy endpoint, which is a composite of confirmed asymptomatic DVT, confirmed symptomatic VTE (symptomatic DVT of the leg or non-fatal pulmonary embolism [PE]), and unexplained death for which PE cannot be ruled out, was designed to comprehensively capture VTE events and has been used in prior post-TKA VTE studies (Verhamme, 2021) (Weitz, 2020) (Weitz, 2021). Asymptomatic DVT is best detected with venography because of its high sensitivity relative to other modalities. In a study that directly compared venography to ultrasound for detection of asymptomatic DVT following hip or knee replacement surgery in patients receiving anticoagulant prophylaxis, the overall incidence of DVT detected by venography was 18.9%, compared to 11.5% with ultrasound (Schellong, 2007). Unilateral venography of the operated leg detects more than 80% of DVTs in patients undergoing unilateral TKA. Relative to bilateral procedure, unilateral venography reduces discomfort and improves compliance with the procedure with relatively limited loss of event detection. Venography is performed at day 10 (± 2 days), based on early studies suggesting that most DVTs form prior to day 12 after surgery (Gallus, 1976).

The safety secondary endpoint was chosen to capture clinically relevant bleeding events. The International Society on Thrombosis and Hemostasis (ISTH) criteria will be used for both major (Schulman, 2010) and CRNM (Kaatz, 2015) bleeds. Both have clear, consensus definitions that will allow for robust adjudication.

Minimal bleeds are not included in the secondary safety endpoint due to lack of clear criteria, which are crucial due to unblinded assignment of treatment. As minimal bleeding occurs more frequently and might therefore be of interest, incidence of minimal bleeding will be tabulated separately as an exploratory endpoint. Minimal bleeding comprises any bleeding AE that does not qualify as either major bleeding or CRNM.

The length of study follow-up is 75 days. Data from study R9933-HV-2107 showed that aPTT had returned within 10% of normal values by Day 64 following a single 300 mg IV dose, which is the dose used in this trial (Section 3.2.2). Both enoxaparin and apixaban will be dosed through the time of venography (or day 12, whichever is earlier); based on their half-lives (enoxaparin 4.5 to 7 hours, apixaban 12 hours), pharmacologically relevant levels are not present a few days after the last dose.

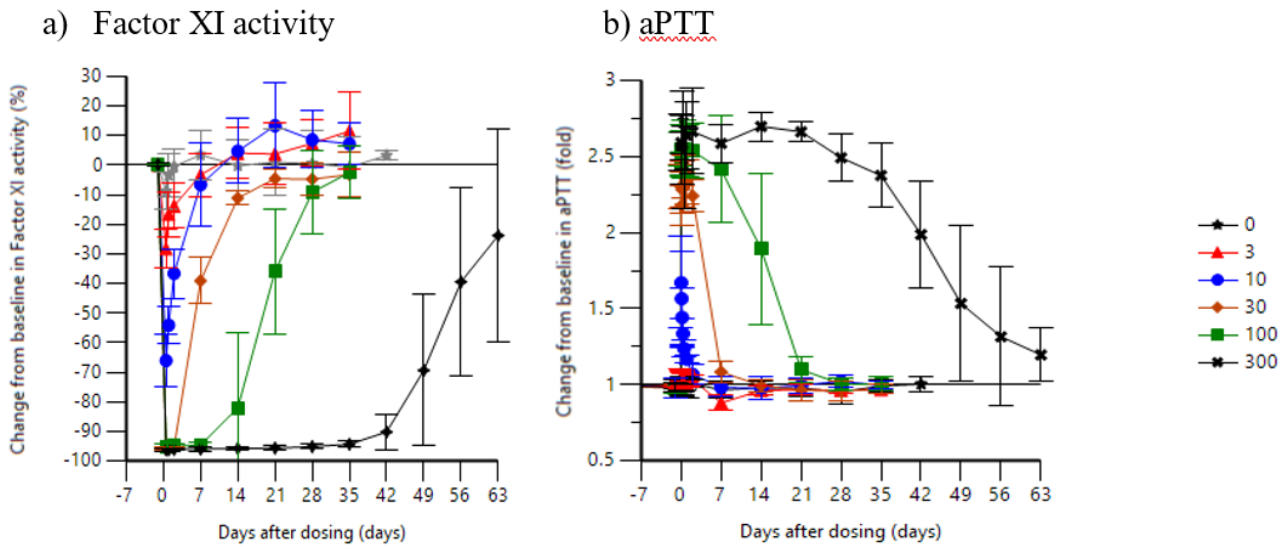
3.2.2. Rationale for Dose Selection

A single 300 mg IV dose of REGN9933 has been chosen based on data from a single ascending dose study with REGN9933 in healthy volunteers (study R9933-HV-2107) which explored the safety, PK, and PD effects, of single IV doses of REGN9933 up to 300 mg. Study participants each received a single 0.5 hour IV infusion of REGN9933 or matching placebo and blood samples for measurement of concentrations of REGN9933 in serum and PD assays (including Factor XI activity, PT and aPTT) were collected at intervals. REGN9933 pharmacokinetics were non-linear across the 3 to 300 mg dose range in a manner consistent with target-mediated drug disposition. REGN9933 treatment had no apparent effect on PT, but produced a rapid, dose-dependent decrease in Factor XI activity and a rapid, dose-dependent increase in aPTT without significant safety, tolerability, or bleeding findings. Preliminary analyses of available data are summarized in Section 5.2 of the IB.

Single doses of REGN9933 ≥100 mg produced sustained inhibition of FXI activity and increases in aPTT in all treated individuals (Figure 1). Based on these observed data it is expected that a REGN9933 dose of 300 mg will maintain maximal inhibition of FXI activity and maximal effects on aPTT (~2.8-fold change from baseline, corresponding to absolute aPTT values of approximately 60 to 80 sec) in all individuals for ≥14 days. Pharmacodynamic data from study R9933-HV-2107 showed that aPTT values had returned to within 10% of normal values 64 days following the 300 mg dose.

REGN9933 exposures from a 300 mg IV dose are substantially lower than corresponding exposures at the non-clinical toxicology no observed adverse effect level (NOAEL). Observed average total REGN9933 exposures from a 300 mg dose in study R9933-HV-2107 were >60× lower than average exposures at the NOAEL dose (100 mg/kg IV) in the 5-week REGN9933 GLP monkey toxicology study (R9933-TX-20070).

Figure 1: Mean (+SD) Change from Baseline in a) Factor XI Activity and b) aPTT by Nominal Time and by Dose in Healthy Volunteers (0-63 Days, Linear Scale, Study R9933-HV-2107)



Arithmetic means, error bars represent standard deviation.

Previous studies investigating the use of FXI inhibitors for prevention of post-operative VTE have shown that efficacy correlates with the magnitude of treatment effects on aPTT; maximum efficacy was achieved at doses which maintained near-maximal increases in aPTT (ie 2 to 3x increase from baseline) throughout the assessment period eg (Verhamme, 2021). It is therefore anticipated that a 300 mg dose of REGN9933 will produce maximal efficacy for prevention of VTE in this clinical setting.

3.3. Risk-Benefit

Recognizing that the "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the Sponsor does not intend to screen any participants in this study until the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and participants can safely participate in this study. Until then, the Sponsor plans to obtain approvals from Health Authorities/Ethics Committees to enable initiation of study sites for this study, as allowed by local laws and regulations.

For information regarding the permitted timing of COVID-19 vaccinations, see Section 7.2.2 Exclusion Criteria, criterion #22, and Section 8.8.1 Prohibited Concomitant Medications and Procedures.

A risk-benefit statement with respect to the overall development program is provided in Section 7 of the IB.

3.3.1. Risk-Benefit for REGN9933

REGN9933 is a monoclonal antibody that binds to FXI and inhibits activation by the intrinsic pathway of the coagulation cascade.

There is no clinical evidence that REGN9933 prevents VTE in post-surgical patients, including TKA. However, several lines of evidence suggest that inhibition of the intrinsic pathway, and FXI specifically, may reduce the incidence of VTE. As discussed in Section 1, FXI deficiency is associated with reduced risk of VTE in humans. Furthermore, clinical studies with other FXI blockers have shown reduced incidence of VTE after TKA relative to enoxaparin (Büller, 2015) (Verhamme, 2021) (Weitz, 2020) (Weitz, 2021). Extrapolation of these data to REGN9933 may be limited since it has a distinct mode of binding to FXI. Single doses of REGN9933 have been studied in healthy volunteers (study R9933-HV-2107) and REGN9933 treatment produced a rapid, dose-dependent decrease in FXI activity and a corresponding rapid, dose-dependent increase in aPTT, indicating inhibition of the intrinsic pathway (refer the Section 5.2 of the IB for preliminary analyses of available data). The magnitude of FXI inhibition and PTT elevation are comparable to those seen with other FXI blockers at doses that reduced VTE after TKA. Furthermore, the key design elements of this study are similar to those in the previous FXI inhibitor trials referenced above.

Post-TKA VTE are generally asymptomatic. In the aforementioned studies comparing FXI targeted therapy versus enoxaparin in post-TKA VTE, <2% of participants experienced a symptomatic VTE. In addition, of all of the participant who experienced a VTE, <15% were symptomatic. Even with placebo, only 13% of patients experienced a proximal DVT after TKA (Lovenox [Package Insert], 2022) .

Mitigation and monitoring for VTE risk include:

- Participant selection will exclude those with history of thromboembolic disease or thrombophilia
- Routine, protocol-specified monitoring for clinical signs of VTE
- Scheduled venogram can identify subclinical DVTs that may be treated with therapeutic anticoagulation

Bleeding is an important potential risk of treatment with any anticoagulant, including REGN9933. As discussed in Section 1, genetic FXI deficiency is not associated with spontaneous bleeding. Clinical studies with other FXI inhibitors have not shown increased risk of bleeding, even when dosed prior to TKA surgery.

To date, no study drug-related AEs or SAEs have been observed with REGN9933 in the healthy volunteer study R9933-HV-2107 (as discussed in Section 1).

In preclinical toxicology studies with cynomolgus monkeys, REGN9933 was administered at doses up to 100 mg/kg via SC injection and 100 mg/kg via IV infusion (once weekly for 5 weeks). There were no significant increases in PT, and bleeding events were similar between treated and non-treated animals.

Mitigation and monitoring for bleeding risk include the following:

- Participant selection will exclude participants with identified bleeding disorders or risk factors for significant bleeding.
- During the trial, participants will be monitored for bleeding events.
- Coagulation parameters will be followed for all participants.
- Moderate to severe bleeding (both spontaneous and non-spontaneous) will be considered adverse events of special interest (AESI) with expedited reporting.
- In the event participants need to seek medical attention during the follow-up period, they are provided a card that details that they are enrolled in a study of a novel anticoagulant targeting FXI upon clinic discharge following surgery.

As described in the Study Stopping Rules (Section 6.1.1.1), the Independent Data Monitoring Committee (IDMC) will monitor the overall rates of both VTE and bleeding, and can recommend pausing of REGN9933 dosing if there are concerns of increased VTE or bleeding risk relative to enoxaparin.

Other important potential safety risks include systemic hypersensitivity reactions, embryofetal toxicity, and immunogenicity. With regard to potential embryofetal toxicity, WOCBP and men whose sexual partners are not willing to practice highly effective contraception are excluded from this study. For more information on mitigation and monitoring for these potential risks, please refer to Section 6 of the IB.

3.3.2. Risk-Benefit for Active Comparator and Calibrator

As with other anticoagulants, participants taking apixaban or enoxaparin are to be carefully observed for signs of bleeding. In countries where enoxaparin and apixaban have been granted marketing authorization, the regulatory bodies have considered that the benefit of therapy has outweighed the risk for the indications granted, including VTE prophylaxis after TKA. All investigators must comply with and satisfy all requirements for the local risk management plan or equivalent for apixaban and enoxaparin where applicable and before dosing participants. In this study, participants will be closely monitored for bleeding, with oversight of the study by the IDMC (Section 6.3.1). Emergent evaluation and management of bleeding should be conducted according to standard local protocols aligned with bleeding management guidelines, as described in Section 8.2.

3.3.2.1. Enoxaparin

Enoxaparin is approved for the prevention of VTE after TKA in the countries in which the trial will be conducted (Inhixa [Summary of Product Characteristics], 2021) (Lovenox [Product Monograph], 2021) In this study, enoxaparin is being administered at the dose recommended by the EU summary of product characteristics (SmPC). While the 40 mg once daily dose is not approved in Canada, it is included as an acceptable regimen in a clinical guide issued by a Canadian vascular medicine professional organization (Thrombosis Canada, 2013) and has been used in several recent similar trials (Weitz, 2020) (Weitz, 2021). Once daily dosing is also expected to improve compliance with dosing. There are no additional benefits and risks to participants apart

from those described in the approved prescribing information for enoxaparin. See Section 3.2.1 for information on the rationale for inclusion of enoxaparin.

3.3.2.2. Apixaban

Apixaban is approved for the prevention of VTE after TKA in the countries in which the trial will be conducted (Eliquis [Summary of Product Characteristics], 2021) (Eliquis [Product Monograph], 2019). In this study, apixaban is being administered at the recommended dose within the approved indication. There are no additional benefits and risks to participants apart from those described in the approved prescribing information for apixaban. See Section 3.2.1 for information on the rationale for inclusion of apixaban.

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

4.1.1. Primary Endpoint

The primary endpoint is the incidence of confirmed, adjudicated VTE (defined in Section 5.2.1) through day 12 (REGN9933 vs enoxaparin).

4.1.2. Secondary Endpoints

The secondary endpoints are:

- Incidence of major bleeding and CRNM bleeding (defined in Section 5.3.1) through time of venography (or day 12, whichever is earlier)
- Incidence of treatment-emergent adverse events (TEAEs) through the end of study
- Incidence of major VTE (defined in Section 5.2.2) through day 12 (REGN9933 versus enoxaparin)
- Incidence of DVT as measured by venography of the operated leg on day 10 ±2 days (REGN9933 vs enoxaparin)
- Concentrations of REGN9933 in serum through end of study
- Change in aPTT from baseline through end of study
- Change in PT from baseline through end of study
- Incidence and titer of anti-drug antibodies (ADA) to REGN9933 through end of study
- Incidence of confirmed, adjudicated VTE through day 12 (enoxaparin vs apixaban)

4.1.3. Exploratory Endpoints

The exploratory endpoints are:

- Incidence of confirmed VTE (defined in Section 5.2.1) through day 12 (REGN9933 vs apixaban) and through the end of study
- Incidence of major VTE (defined in Section 5.2.2) through the end of study
- Incidence of confirmed symptomatic DVT in either leg through day 12 and through the end of the study
- Incidence of confirmed PE through day 12 and through the end of study
- Incidence of fatal PE, which includes sudden death for which PE cannot be ruled out, through day 12 and through the end of study
- Incidence of DVT as measured by venography of the operated leg on day 10 ±2 days (REGN9933 vs apixaban)
- In participants with DVT detected on venogram:
  - distribution of DVT (proximal versus distal)

  - for proximal DVT, size of VTE
  - for distal DVT, the number of veins affected
- Incidence of major bleeding and CRNM bleeding (defined in Section 5.3.1) through end of study
- Incidence of minimal bleeding through time of venography and through the end of study
- Change in measures of coagulation pathway function compared to baseline, including, but not limited to:
  - FXI:C ([Factor XI functional activity] FXI coagulant activity assay)
  - Total FXI concentration
  - Thrombin generation assay (TGA) for extrinsic and intrinsic pathways

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height, etc), disease characteristics, medical history, medication history, baseline aPTT and FXI level, and information on TKA surgery for each participant.

5.2. Efficacy Variables

5.2.1. Confirmed VTE

The primary efficacy variable is adjudicated, confirmed VTE. This is a composite endpoint that includes: asymptomatic deep DVT detected by unilateral venography of the operated leg; confirmed symptomatic DVT of either leg; confirmed fatal or nonfatal PE including unexplained death for which PE cannot be ruled out.

5.2.2. Major VTE

This is a composite endpoint that includes: proximal DVT; confirmed symptomatic DVT of either leg; confirmed fatal or nonfatal PE including unexplained death for which PE cannot be ruled out.

5.3. Safety Variables

The safety variables include physical examination (including weight, temperature, and other vital signs), electrocardiograms (ECGs), laboratory evaluations (hematology, chemistry, urinalysis, other laboratory tests), concomitant medications, bleeding events (major bleeding and CRNM bleeding), and AEs.

5.3.1. Bleeding Events

The ISTH criteria will be used for both major bleeding events and CRNM events as described below. Minimal bleeding will be captured separately as an exploratory endpoint.

Major Bleeding (ISTH):

- Fatal bleeding and/or
- Bleeding that is symptomatic and occurs in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome, assessed in consultation with the surgeon, and/or
- Overt extrasurgical site bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or packed red cells, with temporal association within 24 to 48 hours to the bleeding, and/or
- Surgical site bleeding that requires a second intervention (open, arthroscopic, endovascular) or a hemarthrosis of sufficient size as to interfere with rehabilitation by delay in mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection, and/or

- Surgical site bleeding that is unexpected and prolonged and/or is sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be an associated fall in hemoglobin level of at least 20 g/L (1.24 mmol/L), or transfusion indicated by the bleeding, of at least two units of whole blood or red cells, with temporal association within 24 hours to the bleeding.

Clinically Relevant Non-Major Bleeding (ISTH):

- Any sign or symptom of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria:
  - requiring medical intervention by a healthcare professional
  - leading to hospitalization or increased level of care
  - prompting a face to face (ie, not just a telephone or electronic communication) evaluation

Minimal Bleeding

Any overt bleeding event that does not meet the criteria for either major or CRNM bleeding will be categorized as a minor bleeding event.

5.4. Pharmacokinetic Variables

The PK variable is the concentration of total REGN9933 at each time point. These sampling timepoints are specified in Table 2 and Table 3.

5.4.1. Drug Target Variables

The drug target variable is the concentration of total FXI in plasma at each time point. These sampling timepoints are specified in Table 2 and Table 3.

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and time-point/visit. Samples in this study will be collected at the clinic visits specified in Table 2 and Table 3.

5.6. Pharmacodynamic and Other Biomarker Variables

Activated partial thromboplastin time and PT are the variables for the secondary PD endpoints.

Additional PD and biomarker variables include FXI:C, intrinsic-pathway-triggered thrombin generation, and extrinsic-pathway-triggered thrombin generation. Samples in this study will be collected at the clinic visits specified in Table 2 and Table 3.

The list may be altered or expanded, as it is recognized that more relevant or novel biomarkers may be discovered during the study. The biomarkers studied will be ones believed to be relevant to the understanding of efficacy, pathophysiology of indication, target engagement, mechanism of action, and possible toxicities of REGN9933.

6. STUDY DESIGN

6.1. Study Description and Duration

This is a phase 2 multicenter, multinational, randomized, open label, active-control study of a single dose of IV REGN9933 for prevention of VTE in participants undergoing an elective, unilateral, TKA. An overview of study design is provided in Figure 2.

Participants who are at least 50 years of age and undergoing elective, unilateral TKA will be randomized after surgery to one of 3 treatment arms—REGN9933, enoxaparin, apixaban—in a ratio of 1:1:1, in a parallel manner. Randomization will be stratified based on study site and age (<70 vs ≥ 70 years of age). Approximately 120 participants will be enrolled in each arm, for a total of up to approximately 360 participants in the study.

After providing informed consent, participants will undergo screening, which can occur from approximately day -30 to -1 (day 1 is defined as the day of TKA surgery). Participants will be randomized after completion of surgery to treatment in one of the following groups:

- REGN9933 300 mg IV, once
- Enoxaparin 40 mg subcutaneous (SC), daily
- Apixaban 2.5 mg orally (PO), BID

Dosing with REGN9933 will occur 12 to 24 hours after the end of surgery.

Dosing with enoxaparin or apixaban will begin 12 to 24 hours after the end of surgery and will continue through the day of venography (or day 12, whichever is earlier). Administration of enoxaparin prior to TKA surgery is not permitted in this study (Section 7.2.2 Exclusion criterion 10 and Section 8.8.1). All investigators must comply and satisfy all requirements for the local risk management plan or equivalent for apixaban and enoxaparin where applicable and before dosing participants.

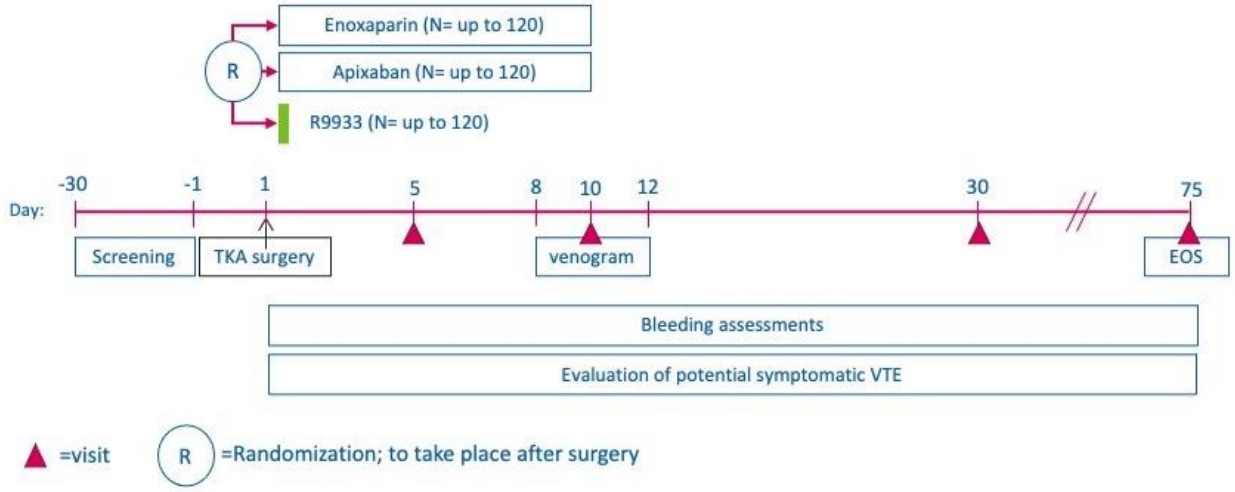
Discharge from the hospital will be determined by the site investigator based on individual participant recovery and local practice. If required, the participant will return to the site for the scheduled assessments, including the mandatory unilateral venography of the operated leg performed on day 10 (±2 days). Prior to site discharge, participants are provided a card detailing that they are enrolled in this study and may be on an FXI inhibitor in the event they need to seek medical attention during the outpatient period.

While in the hospital after surgery and at subsequent study visits, participants will be assessed for signs and symptoms of: symptomatic DVT, including lower extremity swelling, warmth, redness, and pain; PE, including shortness of breath, chest pain exacerbated by inspiration, and hemoptysis; bleeding, either at the surgical site or elsewhere. If DVT is suspected, objective confirmatory testing should be obtained using either lower extremity ultrasound, conventional venography, CT venography, or magnetic resonance (MR) venography, with the choice of modality at the discretion of the investigator. If PE is suspected, objective confirmatory testing should be obtained using spiral CT, ventilation/perfusion scan, or pulmonary angiography, with the choice of modality at the discretion of the investigator. If the confirmatory tests do not demonstrate DVT/PE, or if a distal DVT is demonstrated by ultrasound, then venography should be performed as specified in the protocol. On the other hand, if the presence of DVT (if diagnosed by ultrasound, then DVT

must be proximal) or PE is confirmed prior to the protocol-defined venogram on day 10 (±2 days), then the venogram is not performed.

Participants will continue to be followed until the end-of-study visit on day 75. Assessments will include venography as described above; AE monitoring; physical exams; clinical laboratory testing (hematology, chemistry, coagulation, and urinalysis); ECG; PK, PD and biomarker sampling.

Figure 2: Study Flow Diagram



6.1.1.1. Study Stopping Criteria

The IDMC will monitor unblinded data on an ongoing basis to assess the risk/benefit profile of REGN9933. If at any time the IDMC has significant concerns regarding a meaningful imbalance in VTE incidence, TEAEs, treatment-emergent SAEs, or treatment-emergent AESIs, they may make a recommendation to the sponsor to halt dosing with REGN9933 or make other changes in the study conduct. This will prompt a review by the sponsor who will decide to implement, modify, or reject the recommendation. Applicable regulatory procedures will be adhered to as required by local laws in relation to any decisions related to a change in study conduct, temporary halt, study termination, or study restart.

6.1.2. End of Study Definition

End of study (trial) is the global last participant last visit, withdraws from the study, or is lost to follow-up (ie, the study participant can no longer be contacted by the investigator).

6.2. Planned Interim Analysis

An interim analysis (IA) will be conducted by the Sponsor when there are at least 50 participants per arm who have finished the study. The IA will only be used for administrative purpose and will not be used to make any decisions regarding the conduct of this study, eg, stop the study. Refer to Section 11.5 for further details.

A description of the statistical methods to be employed is in Section 11.4, and blinding implications are discussed in Section 8.6.

6.3. Study Committees

6.3.1. Independent Data Monitoring Committee

The IDMC (also known as a Data Monitoring Safety Board) is an independent, multidisciplinary group consisting of clinicians and statistician(s) that, collectively, have experience in areas relevant to this clinical study and in the conduct and monitoring of randomized clinical studies.

The IDMC is independent from Regeneron and the study investigators and is responsible for reviewing the efficacy and safety data of study participants on an on-going basis in order to provide, in a timely fashion, appropriate recommendations to Regeneron regarding the safety and the welfare of the participants exposed to REGN9933. Based on these reviews in the context of the totality of evidence, the IDMC may make a recommendation to the sponsor to temporarily pause, alter, or terminate the study. Once recommendations from the IDMC have been received, further discussions may be conducted, if appropriate, and the sponsor will determine if these or other actions should be taken.

Details will be provided in the IDMC charter.

6.3.2. Steering Committee

The Steering Committee will be comprised of independent experts, selected by Regeneron. The Steering Committee will provide advice on all scientific matters (including protocol development and publication of results) related to the study.

Details will be provided in the Steering Committee charter.

6.3.3. Adjudication Committee

The AC will be comprised of independent experts selected by Regeneron. The AC will review and determine interpretation and/or classification of the following events and tests in a blinded manner: all imaging procedures used for determination of VTE, including mandatory venography and testing for suspected DVT or PE; all deaths; all suspected bleeding events.

Details will be provided in the Adjudication Committee charter.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PARTICIPANTS

7.1. Number of Participants Planned

Up to approximately 360 participants will be enrolled in the study.

7.2. Study Population

The study population will consist of adults who are at least 50 years of age and undergoing an elective, unilateral TKA.

7.2.1. Inclusion Criteria

A participant must meet the following criteria to be eligible for inclusion in the study:

1. Is a male or female ≥50 years of age at the screening visit, undergoing elective unilateral TKA.
2. Has a body weight ≤130 kg at screening visit.
3. Is judged by the investigator to be in good health based on medical history, physical examination, vital sign measurements, and ECG's performed at screening and/or prior to administration of initial dose of study drug.
4. Is in good health based on laboratory safety testing obtained during the screening period:
    a. Platelet count >150K
    b. Normal PT, international normalized ration (INR), and aPTT during screening
    c. Hemoglobin >10 g/dL
    d. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) < 3X upper level of normal (ULN), or total bilirubin < 2X ULN

    Note: Participants with suspected or confirmed Gilbert's disease can be enrolled in the study
5. Willing and able to comply with clinic visits and study-related procedures including venography.
6. Provide informed consent signed by study participant.

7.2.2. Exclusion Criteria

A participant who meets any of the following criteria will be excluded from the study:

1. Any condition that, as assessed by the investigator, may confound the results of the study or poses an additional risk to the subject by study participation.
2. History of bleeding in the 6 months prior to dosing requiring hospitalization or transfusion; history of intracranial or intraocular bleeding, excessive operative or post-operative bleeding, and traumatic spinal or epidural anesthesia; history of bleeding diathesis (eg, Hemophilia A or B, von Willebrand's Factor deficiency).
3. History of thromboembolic disease or thrombophilia.

4. History of major surgery, including brain, spinal, or ocular, within approximately the past 6 months.
5. History of major trauma within approximately the past 6 months prior to dosing.
6. Hospitalized (>24 hours) for any reason within 30 days of the screening visit.
7. Using the Modification of Diet in Renal Disease (MDRD) equation, has an estimated glomerular filtration rate (GFR) of <45 mL/min/1.73m^2 at the screening visit.

   Note: If subject has a GFR below 45 mL/min/1.73m^2, one repeat test is allowed. Participant may be enrolled if repeat demonstrates GFR of >45 mL/min/1.73m^2.
8. History of hypersensitivity or contraindication (per local label) to any of the study treatments or their excipients.
9. Contraindication to anticoagulation in the opinion of the investigator.
10. Has received or plans to receive preoperative enoxaparin on the day prior to TKA surgery.
11. Allergy to contrast agents, poor venous access, or other factors that might preclude venography.
12. Expected post-operative use of epidural/spinal catheter.
13. Patients who have traumatic epidural/spinal anesthesia or excessive intra-operative blood loss during TKA surgery should not be randomized to receive study treatment.
14. Has a history of alcohol or drug abuse.
15. Known history of human immunodeficiency virus (HIV) infection, or ongoing chronic hepatitis B or hepatitis C infection. Prior resolved hepatitis B infection is not an exclusion.
16. Any malignancy, except for nonmelanoma skin cancer or cervical/anus in situ, that have been resected with no evidence of metastatic disease for 3 years prior to the screening visit.
17. History of significant multiple and/or severe allergies (eg, latex gloves) or has had an anaphylactic reaction to prescription or nonprescription drugs or food.
18. Participated in any clinical research study evaluating another investigational drug including biologics or therapy, including specific immunotherapy, within 90 days or at least 5 half-lives (whichever is longer) of an investigational biologic drug or at least 4 weeks for other investigational drug prior to the screening visit
19. Unwilling or unable to comply with the prohibited medication specifications for this study:
    a. Participants who require therapeutic (full-dose) anticoagulation should be excluded
    b. Participants who require antiplatelet therapy (except for acetylsalicylic acid [ASA] ≤100 mg/day) should be excluded
20. Presents any concern to the study investigator that might confound the results of the study or poses an additional risk to the subject by their participation in the study

21. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the sponsor.
22. Has received a COVID-19 vaccination within 1 week of planned start of study medication or for which the planned COVID-19 vaccinations would not be completed 1 week prior to start of study drug.
23. Sexually active men with WOCBP partners who are unwilling to use medically acceptable birth control through day 75 (end of study [EOS]): vasectomy with medical assessment of surgical success OR consistent use of a condom.
24. Women of childbearing potential*

    *WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

    A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to the Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing and contraception are not required for women who are post-menopausal or permanently sterile.

7.3. Premature Withdrawal from the Study

A participant has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a participant from the study if it is no longer in the interest of the participant to continue in the study, or if the participant's continuation in the study places the scientific outcome of the study at risk (eg, if a participant does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of participants should be avoided.

Participants who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 9.1.2.

Rules for discontinuation of study intervention (permanent or temporary) are discussed in Section 8.3.2.

7.4. Replacement of Participants

Participants prematurely withdrawn from the study can be replaced, if needed, to ensure an adequate number of evaluable participants. The Medical/Study Director, in cooperation with the Study Biostatistician, will decide whether or not to replace a withdrawn participant.

Participants enrolled and withdrawn from study any time prior to first dose of study drug will not be considered evaluable for assessment and will be replaced with another participant. All participants who have received a dose of study drug will be included in an as treated analysis.

8. STUDY TREATMENTS

8.1. Investigational and Reference Treatments

Study interventions are presented in Table 1.

Treatment arms are:

- REGN9933 300 mg IV, single dose administered as 0.5-hour infusion
- Enoxaparin 40 mg SC, daily through the time of venography (or day 12, whichever is earlier)
- Apixaban 2.5 mg PO, BID through the time of venography (or day 12, whichever is earlier)

For REGN9933, a single IV dose will be administered 12 to 24 hours after surgery (>12 hours after removal of the spinal/epidural anesthesia needle/catheter).

For enoxaparin, dosing will begin 12 to 24 hours after surgery (>12 hours after removal of the spinal/epidural anesthesia needle/catheter). Dosing will continue through the time of venography (or day 12, whichever is earlier). If a participant is discharged from the hospital prior to the venogram, the participant may choose to self-administer enoxaparin or have a designated person administer enoxaparin at home. Injection training of enoxaparin will be provided. After training, observation of self-administration/designated person will be conducted by clinical site personnel. Once this observation is considered satisfactory, then the study drug can be subsequently administered independently by the participant/designated person for the remainder of the dosing period.

For apixaban, dosing will begin 12 to 24 hours after surgery (>12 hours after removal of the spinal/epidural anesthesia needle/catheter). Dosing will continue through the time of venography (or day 12, whichever is earlier). Apixaban dosing will continue at home if a participant is discharged from the hospital prior to the venogram.

A patient diary will be provided to record compliance of at-home dosing of enoxaparin/apixaban. The diary should be completed upon each study drug administration.

Instructions on dose preparation are provided in the pharmacy manual.

Table 1: Study Interventions Administered

Intervention Name	REGN9933	Enoxaparin	Apixaban
Intervention Description	300 mg IV, single dose administered as 0.5-hour infusion	40 mg SC, daily through the time of venography	2.5 mg PO, BID through the time of venography
Type	Biologic	Drug	Drug
Dose Formulation	Lyophilized Powder	Pre-filled Syringe-Liquid Solution	Film Coated Tablet
Unit Dose Strength(s)	265 mg in 20 mL vial	40 mg, 0.4 mL, pre-filled syringe	2.5 mg tablets, in a blister pack/wallet carton
Dosage Level(s)	300 mg, once	40 mg, daily, through the time of venography	2.5 mg, BID, through the time of venography
Route of Administration	IV infusion	SC injection	Oral

Use	Experimental	Active Comparator	Active Calibrator
IMP and NIMP/AxMP	IMP	IMP	IMP
Sourcing	Regeneron Drug Supply	Provided centrally by the sponsor. May be locally sourced by sites in Canada	Provided centrally by the sponsor. May be locally sourced by sites in Canada

8.2. Rescue Treatments

8.2.1. Treatment of VTE

Treatment of symptomatic VTE events that occur during the trial will be managed by the investigator per local practice.

For participants receiving either enoxaparin or apixaban, increasing the dose of either agent to therapeutic levels (according to local standards) may be considered. For participants who develop a symptomatic VTE after receiving REGN9933, consideration may be given to DOACs, which have more predictable anticoagulant activity and lower bleeding liability than other anticoagulants. Therapeutic doses of LMWH may also be considered.

Asymptomatic VTE may be monitored with additional imaging assessments at the discretion of the site investigator. In addition, treatment with therapeutic anticoagulation may be considered, depending on the clinical situation, and at the discretion of the site investigator.

8.2.2. Treatment of Bleeding Events

Participants requiring emergent evaluation for bleeding should be first treated with conventional bleeding management per standard protocols, including local compression by either manual compression or pressure bandages applied to the wounds. If bleeding persists, treatment should be provided at the discretion of the treating physician and aligned with local practice and bleeding management guidelines. Participants should be treated with respect to their clinical signs and symptoms of bleeding and not treated per a normalized aPTT/PT laboratory value nor per a specific FXI activity level.

Of note, activated Factor VII (Factor VIIa) products have been reported as successful bypass agents to control bleeding in FXI-deficient patients. Factor VIIa, through multiple portions of the coagulation cascade, contributes to activation of thrombin (Factor IIa) without need for FXI. Factor VIIa is clinically available as recombinant Factor VIIa (rFVIIa) under the brand name NovoSeven (NovoSeven (Summary of Product Characteristics), 2021).

If NovoSeven or another Factor VIIa formulation is available and selected for use at the discretion of the treating physician, the literature has commonly reported NovoSeven doses of 15 µg/kg to 30 µg/kg administered as an IV bolus in FXI-deficient patients. NovoSeven has a half-life of approximately 3 hours and repeat doses of NovoSeven have been reported as administered 2 hours to 6 hours following the first dose depending on surgical and bleeding circumstances. Continuous infusions of rFVIIa at 1.8 µg/kg to 3.6 µg/kg have also been utilized in clinical practice. These lower doses of NovoSeven have been administered with or without anti-fibrinolytics such as tranexamic acid.

Treatment with rescue medications in these events may impact the aPTT and other PD-related endpoints.

8.3. Dose Modification and Study Treatment Discontinuation Rules

8.3.1. Dose Modification

Dose modification of REGN9933 for an individual participant is not allowed.

Sites should follow the enoxaparin and apixaban dosing schedule outlined in Section 8.1. However, enoxaparin and apixaban may be temporarily interrupted or the dose reduced due to medical need, as determined by the investigator.

The criteria for permanent discontinuation of enoxaparin and apixaban are described in Section 8.3.2.2 and Section 8.3.2.3, respectively.

8.3.2. Study Intervention Discontinuation

Participants who permanently discontinue from study intervention (REGN9933, enoxaparin, or apixaban) should be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

Participants who permanently discontinue from study intervention and who opt to withdraw from the study will be asked to complete study assessments, per Section 9.1.2.

8.3.2.1. REGN9933 Discontinuation

As this is a single dose study of REGN9933, discontinuation of REGN9933 is not applicable. Refer to Section 8.4 for the Management of Acute Reactions including interruption and termination of REGN9933 IV infusion.

8.3.2.2. Enoxaparin Discontinuation

Enoxaparin should be discontinued:

- if there is clinical suspicion of HIT
- if there is active clinically significant bleeding

Further management of HIT, the bleeding event, and VTE prophylaxis and is left to the discretion of the investigator.

8.3.2.3. Apixaban Discontinuation

Apixaban should be discontinued:

- if there is active clinically significant bleeding

Further management of the bleeding event and VTE prophylaxis is left to the discretion of the investigator.

8.4. Management of Acute Reactions

8.4.1. Acute Intravenous Infusion Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in Section 10.2.4) and graded using the grading scales as instructed in Section 10.2.5.

8.4.1.1. Interruption of the Intravenous Infusion

The infusion should be interrupted if any of the following AEs are observed:

- Sustained/severe cough
- rigors/chills
- rash, pruritus (itching)
- urticaria (hives, welts, wheals)
- diaphoresis (sweating)
- hypotension
- dyspnea (shortness of breath)
- vomiting
- flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

8.4.1.2. Termination of the Intravenous Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- Anaphylaxis*
- laryngeal/pharyngeal edema
- severe bronchospasm
- chest pain
- seizure
- severe hypotension
- other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc)
- any other symptom or sign that, in the opinion of the investigator, warrants termination of the IV infusion

*Consider anaphylaxis if the following is observed (Sampson, 2006): acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

8.4.2. Acute Injection Reactions

8.4.2.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use. All injection reactions must be reported as AEs (as defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.2.5.

Acute systemic reactions following injection of study intervention (SC) should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

8.4.2.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to Section 10.2.5.

8.5. Method of Treatment Assignment

Participants will be randomized after surgery to one of 3 treatment arms—REGN9933, enoxaparin, apixaban—in a ratio of 1:1:1, according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). Approximately 120 participants will be enrolled in each arm, for a total of up to approximately 360 participants in the study.

Participants will be stratified based on study site and age (<70 vs ≥70 years of age).

8.6. Blinding/Masking

This is a phase 2 multicenter, multinational, randomized, open label, active-control study of a single dose of IV REGN9933 for prevention of VTE in participants undergoing an elective unilateral TKA.

Treatment is administered in an open-label manner because enoxaparin is packaged in pre-filled syringes, making blinding operationally challenging. To mitigate bias in outcome assessment, adjudication of outcomes related to VTE, and bleeding will be performed by a centralized AC that is blinded to treatment assignment (Section 6.3.3).

8.7. Treatment Logistics and Accountability

8.7.1. Packaging, Labeling, and Storage

A medication numbering system will be used to label investigational study drug. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging.

Open-label study drug will display the product lot number on the label.

REGN9933 study drug should be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

Enoxaparin and Apixaban should be stored at the site as follows: Do not store above 25°C (77° F); storage instructions will be provided in the pharmacy manual.

8.7.2. Supply and Disposition of Treatment

All study drug will be shipped at a temperature provided in the pharmacy manual to the investigator or designee at regular intervals or as needed during the study.

At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened REGN9933 will be destroyed with Sponsor's approval or returned to the Sponsor or designee.

At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all centrally sourced opened and unopened enoxaparin and apixaban will be destroyed with Sponsor's approval or returned to the Sponsor or designee

8.7.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each participant
- returned from each participant (if applicable), and
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

8.7.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

8.8. Concomitant Medications and Procedures

Any treatment administered from the time of informed consent to the final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

8.8.1. Prohibited Medications and Procedures

Administration of enoxaparin prior to TKA surgery is prohibited (Section 7.2.2 Exclusion criterion 10).

Anti-platelet therapy (except low doses of ASA ≤100 mg/day) is prohibited, unless indicated for treatment of an AE.

The following procedures/devices are prohibited after study drug has started:

- Use of spinal or epidural analgesia post-operatively
- Pneumatic compression devices

Subjects are prohibited from donating blood products through the EOS visit. Subjects are prohibited from donating sperm through the EOS visit. Subjects are prohibited from having planned, elective surgeries (except for TKA performed on day 1) through the EOS visit.

For patients assigned to the REGN9933 treatment arm, anticoagulant medications (including, but not limited to, vitamin K antagonists, heparins, DOACs) are prohibited after study drug has been started, unless they are indicated for treatment of an AE.

8.8.2. Permitted Medications

Use of standard-of-care medications not listed as prohibited will be allowed.

For subjects assigned to either the enoxaparin or apixaban treatment arm, continued VTE prophylaxis (after completion of protocol-defined treatment, ie through the day of venography [or day 12, whichever is earlier]) is permitted, if deemed necessary by the site investigator based on local guidelines and/or clinical judgment. For the choice of agent to be used for subsequent VTE prophylaxis, it is preferred that the originally assigned treatment (ie enoxaparin or apixaban) is used. However, it is permissible to use other agents, as long as they are consistent with local regulations and standard of care for VTE prophylaxis after TKA surgery.

COVID-19 vaccination and any other vaccination can be administered as deemed necessary per the investigator based on his/her practice, standard of care, or as required based on mandatory vaccination programs. Vaccination is suggested to be administered preferably at least 1 week before the first dose of study drug (Section 7.2.2 Exclusion criterion 22), or at the earliest, 21 days following the last dose of study drug. Live-attenuated vaccines are generally not recommended during the study; however, use is allowed per the investigator's discretion.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct, and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Study assessments and procedures are presented by study period and visit in Table 2.

Definitions

For safety variables, 3 observation periods are defined:

- Screening period - the time from signing the ICF to before the first dose of study drug.
- On-treatment period - the day from first dose of study drug to the date of day 12.
- Follow-up period - the end of the on-treatment period to EOS visit.

Table 2: Schedule of Events

	Screening	On-treatment			Follow-up	
Study Procedure	**Visit 1**	**Baseline Visit 2**	**Visit[1,2] 3**	**Visit[1] 4**	**Visit 5**	**End of Study/ Visit 6**
Day	-30 to -1	1	5	10	30	75
Window (day)			±1	±2	±3	±5
Screening/Baseline:						
Inclusion/Exclusion	X					
Informed consent	X					
Informed consent for pharmacogenomics research (optional)	X					
Informed consent for future biomedical research (optional)	X					
Medical History	X					
Demographics	X					
FSH[3]	X					
GFR (MDRD)	X					
Urine drug screen	X					
Randomization		X[4]				
Treatment:						
TKA		X				
Administer REGN9933		X[5]				
Administer enoxaparin			X[6]			
Administer apixaban			X[6]			
Patient diary (for self-administration of apixaban/enoxaparin)			X			
Efficacy:						
Venography of the operated leg				X		
Assessment for symptomatic VTE[7]		X	X	X	X	X
Safety:						
Height	X					
Weight	X					

	Screening	On-treatment			Follow-up	
Study Procedure	**Visit 1**	**Baseline Visit 2**	**Visit[1,2] 3**	**Visit[1] 4**	**Visit 5**	**End of Study/ Visit 6**
Vital Signs	X	X	X	X	X	X
Physical examination	X	X				X
Electrocardiogram	X					
Assessment for surgical site bleeding		X	X	X		
Assessment for bleeding events		X	X	X	X	X
Adverse events	X	X	X	X	X	X
Concomitant medications and treatment	X	X	X	X	X	X
Laboratory Testing						
Hematology	X	X[8]		X		X
Blood chemistry	X	X[8]		X		X
Coagulation panel	X	X[8]		X		X
Urinalysis	X					X
Pharmacokinetics and Immunogenicity Sampling						
Drug concentration sample (REGN9933)		X[8]	X	X	X	X
ADA (REGN9933)		X[9]				X
Plasma for total FXI concentration		X[8]	X	X	X	X
Biomarkers						
Plasma for aPTT, PT (central lab)		X[8]	X	X	X	X
Plasma for FXI activity (FXI:C) and TGA		X[8]	X	X	X	X
Serum for exploratory research		X[8]	X		X	X
Plasma for exploratory research		X[8]	X		X	X
Optional Pharmacogenomics samples						
Whole blood sample for RNA isolation (optional)[10]		X				X
Whole blood sample for DNA isolation (optional)[10]		X[11]				

ADA: anti-drug antibody; aPTT: activated partial thrombin time; GFR: glomerular filtration rate; FSH: follicle-stimulating hormone; FXI: Factor XI; FXI:C: Factor XI functional activity; MDRD: Modification of Diet in Renal Disease; PT: prothrombin time; TGA: thrombin generation assay; TKA: total knee arthroplasty; VTE: venous thromboembolism

Table 3: Schedule of Events: Visit 2 Blood Collection

Baseline Visit 2 (Day 1)			
Study Procedure	**Pre-operatively**	**Post-operatively**	
		Pre-dosing Up to 1 hour prior to dosing	**Post-dosing** REGN9933 only: as close as possible to 1 hour post-dose
Laboratory Testing			
Hematology	X[1]		
Blood chemistry	X[1]		
Coagulation panel	X[1]		
Urinalysis			
Pharmacokinetics and Immunogenicity Sampling			
Drug concentration sample (REGN9933)		X[2]	X[2]
ADA (REGN9933)		X[2]	
Plasma for total FXI concentration	X[1]	X[3]	X[2]
Biomarkers			
Plasma for aPTT, PT (central lab)	X[1]	X[3]	X[2]
Plasma for FXI activity (FXI:C) and TGA	X[1]	X[3]	X[2]
Serum for exploratory research	X[1]	X[3]	
Plasma for exploratory research	X[1]	X[3]	

ADA: anti-drug antibody; aPTT: activated partial thrombin time; FXI: Factor XI; FXI:C: Factor XI functional activity; PT: prothrombin time; TGA: thrombin generation assay

9.1.1. Footnotes for the Schedule of Events Table

9.1.1.1. Table 2 Schedule of Events

1. Assessments for this visit may be performed in the hospital if the participant has not yet been discharged.
2. If the participant is discharged prior to this visit, then information may be collected by telephone call, and assessments requiring blood draw may be omitted.
3. To be performed in women 55 years of age or younger

4. Randomization will occur after completion of surgery on day 1.
5. Dosing will occur 12 to 24 hours after the end of surgery, and at least 12 hours after removal of the needle/catheter used for spinal/epidural anesthesia.
6. First dose will be given 12 to 24 hours after the end of surgery
7. May include confirmatory studies for DVT of the leg or PE, as described in Section 9.2.2.2. Confirmatory studies for suspected DVT of the leg or PE may be required more than once, per the discretion of the investigator.
8. Refer to Table 3 for detailed information on Visit 2 samples.
9. Samples for ADA must be collected prior to dose administration on the same day that study drug is administrated. Refer to Table 3.
10. The genomics sub-study informed consent form (ICF; for RNA and DNA analysis) must be signed prior to performing this sample collection.
11. Samples for DNA extraction should be collected at the baseline visit (predose) but may also be collected at any later study visit.

9.1.1.2. Table 3 Schedule of Events: Visit 2 Blood Collection

1. Samples may be collected up to 24 hours prior to surgery. Samples to be collected in all 3 treatment groups.
2. Samples to be collected in REGN9933 group only.
3. Samples to be collected in all 3 treatment groups.

9.1.2. Early Termination Visit

Participants who are withdrawn from the study will be asked to return to the clinic once for an early termination visit consisting of the End of Study assessments described in Table 2.

9.1.3. Unscheduled Visits

All attempts should be made to keep participants on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

9.2. Study Procedures

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population:

- Informed consent
- Review of inclusion/exclusion criteria (Section 7.2.1 and Section 7.2.2)
- Medical History
- Demographics

- FSH (women 55 years of age or younger)
- MDRD calculation of eGFR
- Urine drug screen

9.2.2. Efficacy Procedures

9.2.2.1. Venography of the Operated Leg

Unilateral venography of the operated leg will be performed on day 10 (±2 days). Detailed instructions for performing the venography are provided in the Study Imaging Manual for Venography and Event Reporting.

If DVT or PE is suspected at any point during the study, objective confirmatory testing should be carried out as described in Section 9.2.2.2. If the confirmatory tests do not demonstrate DVT/PE, or if a distal DVT is demonstrated by ultrasound, then venography on day 10 (±2 days) should be performed as specified in the protocol. On the other hand, if the presence of DVT (if diagnosed by ultrasound, then DVT must be proximal) or PE is confirmed prior to the protocol-defined venogram on day 10 (±2 days), then the venogram is not performed.

Venograms of low quality and/or venograms with imaging artifacts that cannot be used to confirm presence or absence of DVT will be labeled "non-evaluable". Examples of reasons that contribute to low image quality or artifact include insufficient contrast filling and poor exposure. Detailed instructions for labeling non-evaluable images are provided in the Site Manual for Venography and Event Reporting.

9.2.2.2. Assessment of Symptomatic VTE

While in the hospital after surgery and at subsequent study visits, participants will be assessed by the investigator for signs and symptoms of symptomatic DVT of the leg -- including lower extremity swelling, warmth, redness, and pain—and PE—including shortness of breath, chest pain exacerbated by inspiration, and hemoptysis. If DVT is suspected, objective confirmatory testing should be obtained using either lower extremity ultrasound, conventional venography, CT venography, or MR venography; the test performed will be selected by the investigator. If PE is suspected, objective confirmatory testing should be obtained using spiral CT, ventilation/perfusion scan, or pulmonary angiography; the test performed will be selected by the investigator. The diagnostic tests for symptomatic DVT or PE can be performed per standard of care in the hospital.

Images of the venography and all diagnostic tests performed for suspected symptomatic DVT, or PE should be sent in for central reading. This process is also described in the Study Imaging Manual for Venography and Event Reporting.

9.2.3. Safety Procedures

9.2.3.1. Body Weight

Body weight will be assessed using calibrated scales. Participants should void (empty bladder) prior to weight assessment. Participants should be wearing undergarments only and no shoes during weight assessments. Body weight will be recorded to the nearest 0.1 kg.

9.2.3.2. Height

Participants should not be wearing shoes during height assessment. Height will be recorded to the nearest 1 cm.

9.2.3.3. Vital Signs

Vital signs, including temperature, semi-recumbent blood pressure, pulse, and respiration will be collected time points according to Table 2.

9.2.3.4. Physical Examination

A thorough and complete physical examination will be performed at time points according to Table 2. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the participant's medical history.

9.2.3.5. Electrocardiogram

A standard 12-lead ECG will be performed at time points according to Table 2. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT (identify QTcB or QTcF) intervals will be recorded. The ECG strips or reports will be retained with the source.

9.2.3.6. Assessment for Bleeding

Participants will be assessed for surgical site bleeding events at time points according to Table 2. Description of surgical site bleeding events will include the following: onset and duration; associated clinical symptoms (if any) and sequelae, including prolonged hospitalization or deep wound infection; requirement for additional surgical or interventional procedure

Participants will also be assessed for overall bleeding events at time points according to Table 2. Description of bleeding events will include the following: location; onset and duration; associated symptoms (if any); precipitating factors (if any).

For all bleeding events (surgical and extrasurgical), the following will be recorded: associated changes in hemoglobin, hematocrit; requirement for, timing of, and quantity of transfusion.

In addition, for all participants, peri- and post-operative blood loss will be recorded, as per local practice.

All bleeding events will need to be recorded as an AE with documentation sent to the central AC as instructed in the Study Manual for Venography and Event Reporting. Events will be classified by the AC using the ISTH criteria for both major (Schulman, 2010) and CRNM (Kaatz, 2015) bleeds as described in Section 5.3.1.

9.2.3.7. Laboratory Testing

Hematology, chemistry, urinalysis, and the coagulation panel will be analyzed by local laboratory. Plasma for PT and aPTT biomarkers will be analyzed by a central laboratory. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at visits according to Table 2. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total bilirubin (check direct and indirect if total is elevated)
Potassium	Creatinine	
Chloride	Blood urea nitrogen	
Carbon dioxide	AST	
Calcium	ALT	
Glucose	Alkaline phosphatase	
Albumin		

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Urinalysis*

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

* dipstick urinalysis should be performed initially, with subsequent analysis by microscopy if dipstick is abnormal

Other Laboratory Tests

- FSH (women 55 years of age or younger)
- MDRD calculation of GFR
- Urine drug screen
- Coagulation panel: PT/INR, aPTT. Note these are performed at the local lab; separate samples are collected for PT/INR and aPTT for analysis at a central laboratory (Section 9.2.6).

Refer to the laboratory manual for collection procedures.

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations

should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 10.1.1.

9.2.4. Drug Concentration and Total Factor XI Measurements

Samples for REGN9933 concentration measurement and samples total FXI concentration measurements will be collected at visits listed in Table 2 and Table 3 . Detailed instructions for blood sample collection are provided in the laboratory manual.

Any unused samples may be used for exploratory research, biomarker research and/or future biomedical research as described in Section 9.2.6.4 and Section 9.2.7.

9.2.5. Immunogenicity Measurements and Samples

Samples for ADA assessment will be collected at time points listed in Table 2 and Table 3. Detailed instructions for blood sample collection are provided in the laboratory manual.

Any unused samples may be used for exploratory research and/or future biomedical research as described in Section 9.2.6.4 and Section 9.2.7.

9.2.6. Pharmacodynamic and Exploratory Biomarker Procedures

This study includes measurements of aPTT, PT, as well as the exploratory coagulation endpoints FXI:C and intrinsic- and extrinsic-pathway triggered thrombin generation assessed by TGA.

The main PD variable aPTT will be used to measure the anticipated anticoagulant effect of REGN9933. Prothrombin time is a measure of extrinsic and/or common pathway function. Both FXI:C and TGA are used to measure the inhibition of FXI.

9.2.6.1. Activated Partial Thromboplastin Time and Prothrombin Time

Activated partial thrombin time is a standard clinically validated measure of intrinsic/common pathway activation. Elevations of aPTT in the context of disruption to the intrinsic coagulation pathway are anticipated and are not considered a safety signal since elevations are not necessarily associated with bleeding risk. Activated partial thromboplastin prolongation has been used to monitor REGN9933 effect in the healthy volunteer study R9933-HV-2107. Samples for aPTT measurements will be collected at time points listed in Table 2 and Table 3. Change from baseline in aPTT is a secondary endpoint and considered the main PD variable. Prothrombin time is a standard clinically validated measure of extrinsic/common pathway function. Factor XI deficiency does not affect PT time, and interim data from the healthy volunteer study R9933-HV-2107 suggest that REGN9933 does not alter PT. Samples for PT measurements will be collected at time points listed in Table 2 and Table 3. Change from baseline in PT is a secondary endpoint.

9.2.6.2. Factor XI Functional Activity Levels

Factor XI functional activity is a clinically validated assessment of intrinsic pathway coagulation utilizing a one-stage clotting assay, but unlike aPTT, it is a more specific measure of FXI activity and its contribution to coagulation. FXI:C will be measured from samples collected at time points indicated in Table 2 and Table 3. Modulation of FXI:C is an exploratory measure.

9.2.6.3. Thrombin Generation Assay

Thrombin generation assay is an in vitro and ex vivo assessment of coagulation through both the intrinsic and extrinsic pathways and provides an estimation of the ability to generate thrombin. Thrombin generation assay is not routinely used to monitor anticoagulation clinically but complements other clinically validated coagulation assessments and is useful to determine the risk of bleeding or thrombosis. Thrombin generation is an essential process of coagulation because thrombin is responsible for the activation of other coagulation factors and propagation of additional thrombin (via FXI activation) for the conversion of fibrinogen to fibrin. Using tissue factor or ellagic acid as the trigger in the TGA can provide an estimation of the thrombin being generated by the extrinsic/common pathway and the intrinsic/common pathway, respectively. Thrombin generation will be measured from samples collected at time points indicated in Table 2 and Table 3. Change from baseline in thrombin generation is an exploratory endpoint.

9.2.6.4. Exploratory Biomarkers

Serum and plasma will be collected at time points according to Table 2 and Table 3. These samples may be used to measure biomarkers related to the pathophysiology of VTE, mechanism of action for REGN9933, biology of FXI and related pathways, and possible toxicities.

Any unused samples, collected for any purpose in this study, may be used for exploratory research, as allowed per local regulation.

Biomarker results will be reported separately from the clinical study report (CSR) unless biomarker measurements are included in primary or secondary objectives.

9.2.7. Future Biomedical Research (Optional)

Participants who agree to participate in the future biomedical research (FBR) sub-study will be required to consent to this optional sub-study before samples are banked for FBR. Residual biomarker samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). The samples may be utilized for FBR that may or may not be directly related to the study, including being used as reference samples and assay development or validation. The results of these future biomedical research analyses will not be presented in the CSR.

9.2.8. Pharmacogenomic Analysis (Optional)

Participants who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of the samples. Whole blood samples for DNA extraction should be collected on day 1/baseline (predose) but can be collected at a later study visit. Whole blood samples for RNA extraction will be collected at time points according to Table 2 and

Table 3. DNA and RNA samples will be collected for pharmacogenomics analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study and the molecular basis of coagulation FXI, thromboembolic diseases, and related diseases. These samples will be single-coded as defined by the ICH guideline E15. Samples will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). If there are specific site or country requirements involving the pharmacogenomic analyses which the sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to REGN9933, other thromboembolic clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression of thromboembolic diseases as well as related bleeding disorder-related diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, or thromboembolic diseases and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, and transcriptome sequencing (or other methods for quantitating RNA expression) may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection, from the time of signing the ICF to the end of study (see Section 11.4.5.1). Medical conditions that existed or were diagnosed prior to the signing of the Informed Consent will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of Informed Consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the participant. Adverse events may be directly observed, reported spontaneously by the participant, or by questioning the participant at each study visit. Participants should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. The Investigator should follow up on SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of the on-treatment period) that the Investigator assesses as related to study drug should also be reported.

All AEs, SAEs, AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

10.1.2.1. Individual Case Safety Reporting (ICSR)

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the (when applicable: blinded) study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc) will be summarized in the narrative on the AE CRF and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.2.2. Aggregate Safety Reporting (Development Safety Update Report)

Relevant safety information on the comparators will be addressed in the REGN9933 Development Safety Update Report.

10.1.3. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- **SAEs**.
- **Selected Adverse Events of Special Interest** (serious and nonserious)**:** Adverse events of special interest for this study include the following:
  - Moderate or severe infusion reactions
  - Moderate or severe hypersensitivity reactions potentially related to study treatment
  - Moderate to severe bleeding (both spontaneous and non-spontaneous)
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female or female partner of a male , during the study or within 75 days of the dose of REGN9933, and within 3 days of the last dose of comparators enoxaparin and apixaban. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

- **Symptomatic overdose:** Accidental or intentional overdose of at least 2 times the intended dose of study treatment within the intended therapeutic window, if associated with an AE.

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a participant administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH, 1994).

For studies with patient reported outcomes (PRO), the PRO data are generally not reportable as individual AEs and thus will not be reported or reconciled as such.

10.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a participant is a passenger).
- Is **life-threatening** – in the view of the investigator, the participant is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. Inpatient hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

10.2.4. Infusion Reactions

Infusion reactions are defined as any relevant AE that occurs during the infusion or within 2 hours after the infusion is completed.

10.2.5. Severity

The severity of AEs will be graded according to the following scale:

Mild: Does not interfere in a significant manner with the participant normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms but may be given because of personality of the participant.

Moderate: Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.

Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health. Treatment for symptom may be given and/or participant hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

Infusion Reactions

The severity of infusion reactions will be graded according to the following scale (semi-colon indicates "or" within description of the grade):

Mild: Mild transient reaction; infusion interruption not indicated; intervention not indicated.

Moderate: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.

Severe: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae; life-threatening consequences; urgent intervention indicated; death.

Injection Site Reactions

The severity of injection site reactions will be graded according to the following scale (semi-colon indicates "or" within description of grade:

Mild: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity

Moderate: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity

Severe: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires ER visit or hospitalization; necrosis or exfoliative dermatitis

10.2.6. Causality

The investigator must provide causality assessment as whether or not there is a reasonable possibility that the drug caused the adverse event, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset vs time drug was administered
- Nature of the reactions: immediate vs. long term
- Clinical and pathological features of the events
- Existing information about the drug & same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction
- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

    or

  - The AE follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug under study or its class of drugs or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:

  - The AE follows a reasonable temporal sequence from a protocol specified procedure and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

- Not Related:
  - The AE does not follow a reasonable sequence from a protocol specified procedure or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

The investigator will monitor the safety of study participant at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The Medical/Study Director will have primary responsibility for the emerging safety profile of the compound, but will be supported by other departments (eg, Global Patient Safety; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

10.4. Notifying Health Authorities, Institutional Review Board /Ethics Committee, and Investigators

During the study, the sponsor and/or the contract research organization (CRO) will inform health authorities, IECs/IRBs, and the participating investigators of any SUSARs (Suspected Unexpected Serious Adverse Reactions) occurring in other study centers or other studies of the active study drug (REGN9933; an FXI binder), as appropriate per applicable reporting requirements, including Regulation EU No 536/2014. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the Institutional Review Board (IRB)/Ethics Committee (EC) unless delegated to the sponsor.

Event expectedness for REGN9933 is assessed against the Reference Safety Information section of the Investigator's Brochure that is effective for expedited safety reporting.

Event expectedness for enoxaparin and apixaban is assessed against the SmPC.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the CSR to health authorities and IECs/IRB as appropriate.

11. STATISTICAL PLAN

11.1. Statistical Hypothesis

The clinical hypothesis comparing the efficacy of REGN9933 to enoxaparin or apixaban will be assessed through a Bayesian estimation framework. Bayesian posterior probabilities will be reported to estimate the incidence of confirmed VTE for participants treated with REGN9933 and enoxaparin, as well as the odds ratio (OR) of confirmed VTE in participants administered REGN9933 as compared to that of enoxaparin (OR_{RE}). The statistical hypothesis is $OR_{RE} < 1$.

Specifically, the following will be reported:

- Probability that REGN9933 has a lower incidence of confirmed VTE through day 12 as compared to enoxaparin, ie the probability that the OR of VTE in REGN9933 versus enoxaparin, $Pr(OR_{RE}<1)$. Other quantities will be used to estimate the magnitude of effect, eg $P(OR_{RE} < 0.5, 0.8, 0.9, \text{etc.} \mid \text{data})$

11.2. Justification of Sample Size

Up to total of approximately 360 participants will be randomized in a 1:1:1 allocation ratio to REGN9933, apixaban or enoxaparin. Each arm will have an approximate number of 120 participants.

The sample size was determined using the following assumptions:

- The event rate of VTE for REGN9933 was assumed to be 13% and was set to be 22.4% for enoxaparin (Verhamme, 2021) (Weitz, 2020).
- The prior distribution of the treatment difference, was assumed to be log(OR)~N(0,0.843), which was expressed as the log(OR). The prior distribution follows a normal distribution centered around no treatment difference and with a variance such that extreme treatment differences are expected to be unlikely, ie, the probability that OR is between 0.25 and 4 is 90%.

Using these assumptions, and for the purpose of choosing a sample size, the following quantities were simulated:

- The probability of any beneficial effect of REGN9933 over enoxaparin, ie, the posterior distribution of the odds ratio comparing REGN9933 to enoxaparin of confirmed VTE. A beneficial effect is where $OR_{RE} < 1$, and thus the study will estimate $P(OR_{RE} < 1 \mid \text{data})$.
- In 75% of the simulated trials, in studies where the $P(OR_{RE} < 1 \mid \text{data}) > 0.95$, the sample size was 120 participants or less. Therefore, a sample size of 120 subjects per group was chosen.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets

The primary analysis will be conducted in the modified intention to treat population (mITT) population, consisting of randomized participants that have either an evaluable venogram, a

confirmed episode of venous thromboembolism, or both. A sensitivity analysis will be conducted on the full analysis set (FAS) that includes all randomized participants who received any study drug; it is based on the treatment allocated (as randomized).

11.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized participants who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

11.3.3. Pharmacokinetic Analysis Sets

The PK analysis population includes all participants in the REGN9933 treatment group who received study drug and who had at least 1 non-missing result following the first dose of study drug.

11.3.4. Immunogenicity Analysis Sets

The ADA analysis set includes all participants who received study drug and had at least 1 non-missing ADA result following the first study dose.

11.3.5. Pharmacodynamic Analysis Set

The pharmacodynamic analysis set includes all randomized participants who received any study drug and who had a at least 1 non-missing PD result following the first dose of study drug; it is based on the treatment received (as treated).

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of participants reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

11.4.1. Participant Disposition

The number and percentage of participants screened, randomized, and the primary reasons for screening failure and discontinuation will be summarized.

11.4.2. Demography and Baseline Characteristics

Demographic variables (eg, age, race, and gender), baseline characteristics, medical history, and prior and concomitant mediations and therapies will be summarized by treatment group. See Section 5.1 for a full list of demographic and baseline variables. No statistical hypothesis tests will be performed on these characteristics.

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis

The treatment effect will be estimated using the posterior distribution of OR_{RE}. For comparison of REGN9933 versus enoxaparin, different posterior probabilities will be provided, such as P(OR<0.5, 0.9, 1.0, 1.1, 1.2 etc|data).

The entire posterior density function for the treatment effect (OR_{RE} and the OR of confirmed VTE in participants administered REGN9933 as compared to that of apixaban) will be computed, along with the cumulative posterior distribution, which quantifies evidence for all possible treatment effects. A prior for treatment difference log(OR)~N(0,0.843) will be used. Bayesian summary statistics including two-sided 95% Highest Density Interval, posterior mean, and median will be reported. Summary statistics based on the raw data including the number of participants reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum will be reported.

The Kaplan-Meier plot for cumulative incidence of confirmed VTE over time will be provided by treatment groups. Participants dropped out before the venogram or with missing venograms are considered as censored.

11.4.4. Control of Multiplicity

Not applicable.

11.4.5. Safety Analysis

Safety will be assessed by clinical and statistical review of all relevant parameters, including vital signs, physical examinations, ECGs, laboratory evaluations, and AEs.

11.4.5.1. Adverse Events

Definitions

For safety variables, the 3 observation periods are defined in Section 9.1. Treatment-emergent adverse events are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition after the dose administrations.

Analysis

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of participants with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.2.5), presented by SOC and PT
- Treatment-emergent AESIs
- Treatment-emergent adverse events leading to permanent treatment discontinuation will be summarized by treatment group.

11.4.5.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized.

Laboratory Tests

Laboratory test results will be summarized.

Number and percentage of participants with a potentially clinically significant value will be tabulated.

11.4.5.3. Treatment Exposure

The duration of exposure during the treatment period will be presented by treatment group and calculated as:

- For participants assigned to the enoxaparin or apixaban arm, exposure will be summarized by the number of days that the subject received enoxaparin or apixaban administrations.

11.4.5.4. Treatment Compliance

The compliance with study treatment will be calculated as follows:

$$compliance\ \% = 100\% \times \frac{number\ of\ actual\ administrations}{number\ of\ planned\ administrations}$$

The number of planned administrations will be calculated as:

- For participants assigned to the enoxaparin arm, the number of planned administrations is the number of days in the on-treatment period
- For participants assigned to the apixaban arm, the number of planned administrations is two times of the number of days in the on-treatment period
- For participants assigned to the REGN9933 arm, the number of planned administrations is one

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

The PK parameters may include, but are not limited to:

- C_{max} – peak concentration
- AUC_{last} -area under the curve computed from time zero to the time of the last positive concentration

The concentrations of total REGN9933 over time and selected PK parameters will be summarized by descriptive statistics for each of the treatment groups for the purpose of estimating exposures in these groups. This descriptive statistical assessment will include the geometric means and ratios of the geometric means for selected PK parameters, as deemed appropriate.

No formal statistical hypothesis testing will be performed.

11.4.7. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA response observed:

- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline, with all post-dose ADA results negative, or a positive assay response at baseline, with all post-dose ADA assay responses less than 9-fold over baseline titer levels
- Treatment-emergent ADA response, defined as any post-dose positive ADA assay response when the baseline results are negative
- Treatment boosted ADA response, defined as any post-dose positive ADA assay response that is 9-fold over baseline titer levels when baseline is positive in the ADA assay
- Maximum ADA Titer values
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)

Listings of pre-existing, treatment-boosted, and treatment-emergent ADA responses, ADA titers positivity presented by participant, time point, and dose cohort will be provided. Incidence of treatment-emergent ADA will be assessed as absolute occurrence (N) and percent of participants (%), grouped by study cohorts and ADA titer level.

Plots of drug concentrations will be examined and the influence of ADAs on individual PK profiles evaluated. Assessment of impact of ADA on safety and efficacy may be provided.

11.4.8. Analysis of Pharmacodynamic and Exploratory Biomarker Data

The PD biomarker population will consist of all subjects in the PD analysis set.

For biomarkers including FXI:C and thrombin generation (following intrinsic and extrinsic pathway activation), the following descriptive data will be generated: raw data at baseline, by treatment group, and overall. Biomarkers measured post-treatment will be summarized over time; change and/or percent change from baseline to each scheduled assessment time will be summarized by treatment with descriptive statistics.

Additional details on the biomarker analyses will be provided in the statistical analysis plan.

11.5. Interim Analysis

An IA will be conducted by the sponsor when there are at least 50 participants per arm who have finished the study. The timing of IA was determined for the minimal number of subjects required to observe a high probability that REGN9933 reduced confirmed VTE relative to enoxaparin, ie the smallest sample size where the posterior probability could be at least 90%, ie, $Pr(OR_{RE} \leq 1 \mid data) \geq 90\%$.

The IA will only be used for administrative purpose and will not be used to make any decisions regarding the conduct of this study, eg, to stop the study.

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted, and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s) including Regulation EU No 536/2014 in the EU. The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, releasing) will be maintained and stored at Regeneron (Sponsor).

Adverse events and medical history will be coded using MedDRA. A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical history/surgical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC), Medidata Rave

12.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System – statistical review and analysis
- Pharmacovigilance safety database

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

Regeneron uses a study-specific risk-based approach to study monitoring and oversight, aligned with risk-based quality principles, outlined in ICH E6 (R2) Guideline for Good Clinical Practice. Risk-Based Quality Monitoring (RBQM) methodology focuses on employing a fit-for-purpose monitoring strategy, supported either directly by Regeneron as sponsor, or via our CRO partners. RBQM strategies include: reduced source data verification, targeted source data review, the use of off-site/remote and triggered on-site monitoring visits, and Centralized Monitoring to identify site level risks and study level trends. The investigator must allow study-related monitoring activities to occur.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents,

that the safety and rights of participants are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate participant records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and CRF data are timely, accurate and complete.

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic Case Report Forms (CRFs) within the EDC system by trained site personnel. All required CRFs must be completed for each, and every participant enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each participant, the investigator must provide an electronic signature. A copy of each participant CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In

addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRF must be signed electronically by the investigator. This signed declaration accompanies each set of participant final CRF that will be provided to the sponsor.

12.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer, if a longer period is required by relevant regulatory authorities. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification) and the relevant records will be transferred to a mutually agreed-upon destination.

12.4.3. Recruitment Strategy

Potential study participants may be identified by the investigator through a variety of means, such as publicizing the trial or using existing patient lists. Recruitment resources may include, but are not limited to, recruitment flyers, brochures, social media ads, newspaper ads, radio ads, etc. A third-party vendor may assist in recruitment efforts, such as the development of recruitment materials. All patient-facing recruitment material, including media advertising and receptionist scripts, will be reviewed and approved by the appropriate IRB/EC/authority prior to use. Resources may be in paper or electronic form. Regeneron will not access any patient identifiable information as part of recruitment efforts.

12.4.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the

sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC -approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each participant prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the participant in language that he/she can understand. The ICF should be signed and dated by the participant and by the investigator or authorized designee who reviewed the ICF with the participant.

- Participants who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Participants who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the participant's study record, and a copy of the signed ICF must be given to the participant.

If new safety information results in significant changes in the risk/benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study participants must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the participant's study record and a copy must be given to the participant.

13.3. Participants Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study participant will be maintained. Participants should be identified by a participant identification number only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The participant's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the participants (eg, advertising) before any participant may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the participant, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of participants or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial registries according to applicable local guidelines and regulations. For data integrity, scientific, and statistical reasons, published results from all participants will be disclosed following End of Study (Section 6.1.2). Treatment codes will be disseminated to each investigation site thereafter.

For purposes of data disclosure, interim analyses included in a CSR will be available for disclosure when required by local regulations. If the integrity of the ongoing study cannot be ensured or study blinding cannot be maintained, then only final results will be disclosed.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSEOUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any participant within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of participants required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the participants' interests.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

19. REFERENCES

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Phase 2, Multicenter, Randomized, Open-Label, Active-Control Study of REGN9933, a Factor XI Monoclonal Antibody, for Prevention of Venous Thromboembolism after Elective, Unilateral, Total Knee Arthroplasty and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study Title: A Phase 2, Multicenter, Randomized, Open-Label, Active-Control Study of REGN9933, a Factor XI Monoclonal Antibody, for Prevention of Venous Thromboembolism after Elective, Unilateral, Total Knee Arthroplasty

Protocol Number: R9933-DVT-2230

Protocol Version: R9933-DVT-2230 Amendment 1

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

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