STATISTICAL ANALYSIS PLAN
VERSION: 1.0

CLINICAL STUDY PROTOCOL 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

Compound: **REGN9933**

Protocol Number: **R9933-DVT-2230 Amendment 1**

Clinical Phase: **Phase 2**

Sponsor: **Regeneron Pharmaceuticals, Inc.**

Study Biostatistician: [redacted]

Clinical Trial Manager: [redacted]

Study Medical Director: [redacted]

Version/Date: **Original Statistical Analysis Plan / 02AUG2023**

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Clinical Phase:	Phase 2
Sponsor:	Regeneron Pharmaceuticals, Inc.
Versions/Dates:	Original Statistical Analysis Plan / 02AUG2023

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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
ATC	Anatomical therapeutic chemical
AUC_{last}	Area under the curve computed from time zero to the time of the last positive concentration
BID	Twice daily
BMI	Body mass index
BUN	Blood urea nitrogen
Cmax	Peak concentration
CMH	Cochran-Mantel-Haenszel
CRNM	Clinically relevant non-major
DOAC	Direct oral anticoagulants
DNA	Deoxyribonucleic acid
DVT	Deep venous thrombosis
ECG	Electrocardiogram
EOT	End of test
EOS	End of study
ET	Early termination
FAS	Full analysis set
FSH	Follicle stimulating hormone
FXI	Factor XI
FXIIa	Factor XIIa
FXI:C	Factor XI functional activity
GFR	Glomerular filtration rate
IA	Interim analysis
ICF	Informed consent form
ICH	International Conference for Harmonisation
ID	Identification
ISTH	International Society on Thrombosis and Hemostasis
INR	International normalized ration

IV	Intravenous
LOQ	Limit of quantification
MCMC	Markov Chain Monte Carlo
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
OR	Odds ratio
OR_{RE}	the odds ratio of confirmed VTE in participants administered REGN9933 as compared to that of enoxaparin
PCSV	Potentially Clinically Significant Value
PD	Pharmacodynamic(s)
PE	Pulmonary embolism
PK	Pharmacokinetic(s)
PRO	Patient reported outcomes
PT	Prothrombin time
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RNA	Ribonucleic acid
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
TD	Target day
TE	Treatment-emergent
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
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for analyses prior to database lock. The SAP is intended to be a comprehensive and detailed description of the statistical methods, timing of analyses and analysis presentation to be used in the analysis of data for study R9933-DVT-2230.

This plan may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. The final plan, if revised, will document all changes and be issued prior to database lock.

1.1. Study Description and Objectives

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.

REGN9933 is a monoclonal antibody which binds to FXI and prevents its activation by FXIIa. 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 has been evaluated in a randomized, double-blind, placebo-controlled phase 1 clinical study in healthy volunteers (R9933-HV-2107). 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 2.7-fold at 300 mg IV dose levels. 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 Phase 2, multicenter, randomized, open-label, active-control study is designed to evaluate the efficacy and safety of REGN9933 for prevention of venous thromboembolism (VTE) in participants undergoing an elective, unilateral, total knee arthroplasty (TKA), which is a commonly used clinical setting to demonstrate proof-of-concept of the antithrombotic effects of novel anticoagulants.

Additional information on the background is described in the study protocol.

1.1.1. 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.

1.1.2. Secondary Objectives

The secondary objectives of the study are:To evaluate the bleeding risk (i.e., 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 (i.e., 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

1.2. 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 (i.e., 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 participants

1.3. 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 $OR_{RE} < 1$, i.e. that incidence of confirmed VTE is lower in the REGN9933 arm compared to the enoxaparin arm.

1.4. Modifications from the Statistical Section in the Final Protocol

There is no modification from the statistical section in the final protocol.

1.5. Revision History for SAP Amendments

This is the original version of the SAP.

2. INVESTIGATION PLAN

2.1. Study Design

The study consists of the following periods: a screening period (day -30 to day -1) and a 75-day open-label treatment and follow-up period with REGN9933 or enoxaparin or apixaban. 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:

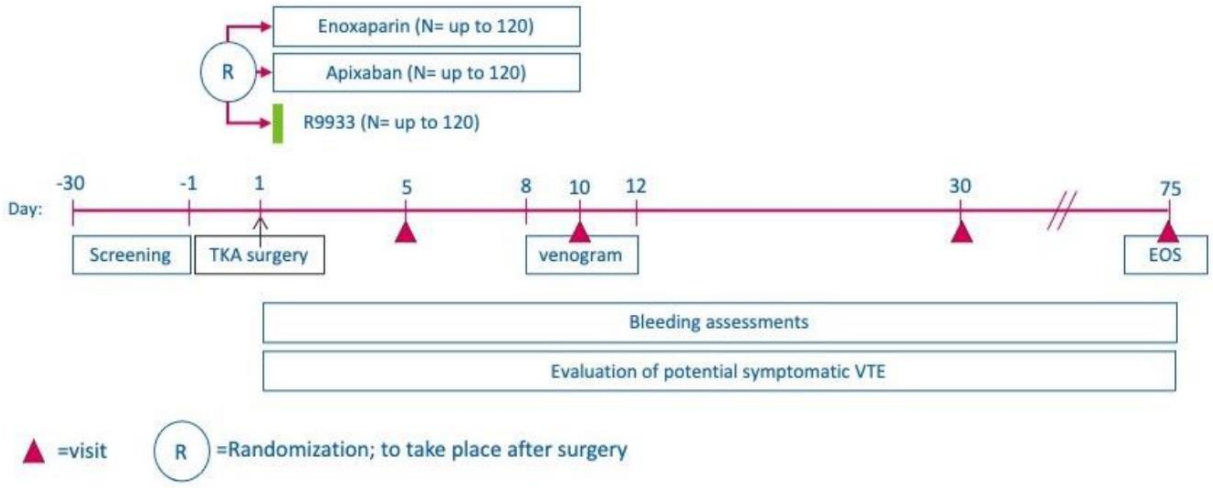
- REGN9933 300 mg IV, once
- Enoxaparin 40 mg subcutaneous (SC), daily through the time of venography or day 12, whichever is earlier
- Apixaban 2.5 mg orally (PO), BID, daily through the time of venography or day 12, whichever is earlier

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 (see protocol 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.

Below is the study flow diagram depicting the different periods of the study with the scheduled visits and treatment administrations.

Figure 1: Study Flow Diagram



2.2. Sample Size and Power Considerations

Approximately 360 participants will be randomized in a 1:1:1 allocation ratio to REGN9933, apixaban or enoxaparin. Each arm will have approximately 120 participants.

The sample size was determined through Bayesian approach. The treatment difference was expressed as the log(OR), and the prior distribution of the treatment difference was assumed to be N(0,0.843), which follows a normal distribution centered around no treatment difference and with a variance such that extreme treatment differences are expected to be unlikely, i.e., 90% probability that OR is between 0.25 and 4.0.

The probability of any beneficial effect of REGN9933 over enoxaparin can be assessed by 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 $Prob(OR_{RE} < 1 \mid data)$.

The sample size of 120 patients per arm was determined through 10000 trial simulation, assuming confirmed VTE event rates of 13% for REGN9933 and 22.4% for enoxaparin. (Enoxaparin rates taken from (Verhamme, 2021) (Weitz, 2020). Out of the 10000 simulated trials, 75% of the simulated trials with $Prob(OR_{RE} < 1 \mid data) > 0.95$ have the sample size of 120 or less.

3. ANALYSIS SETS

The following defines the set(s) of participants whose data will be used for statistical analysis.

3.1. Efficacy Analysis Set

The primary analysis will be conducted in the modified intention to treat population (mITT) population, consisting of randomized and treated participants that have either an evaluable venogram, a confirmed episode of venous thromboembolism, or both through day 12. It is based on the treatment allocated (as randomized).

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.

3.3. Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PK) 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.

3.4. Immunogenicity Analysis Sets

The ADA analysis set (AAS) includes all participants who received study drug (REGN9933) and had at least 1 non-missing ADA result following the first study dose.

3.5. Pharmacodynamic Analysis Sets

The pharmacodynamic analysis set (PDAS) 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).

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic variables will be summarized by treatment group:

- Age at screening (year)
- Age categories (<70, ≥ 70)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic/Latino, Not Hispanic or Latino)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m2)

Other baseline characteristics may include:

- Medication history (antiplatelets; NSAIDs; hormone replacement therapy)
- aPTT (sec)
- PT (sec)
- FXI functional activity level
- TKA information (including but not limited to operative leg, blood loss during surgery, and type of anesthesia)

4.2. Medical History

Medical histories will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA).

4.3. Prior / Concomitant Medication

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.

Medications will be recorded from the day of informed consent until the end of study (EOS) visit. Medications will be coded to the anatomical therapeutic chemical (ATC) classification level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD). Participants will be counted once in all ATC categories linked to the medication.

Prohibited concomitant medications/procedures

Administration of enoxaparin prior to TKA surgery is prohibited (see protocol Section 7.2.2 Exclusion criterion 10, and Section 8.8.1).

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

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

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

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

For participants 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.

4.4. Efficacy Variables

4.4.1. Primary Efficacy Variable

The primary endpoint is adjudicated, confirmed VTE through day 12. This composite endpoint consists of: asymptomatic deep DVT detected by unilateral venography of the operated leg; confirmed symptomatic DVT of either leg; confirmed fatal or nonfatal pulmonary embolism (PE) including unexplained death for which PE cannot be ruled out.

Adjudicated VTE outcomes are generated by the Adjudication Committee that will review and determine interpretation and/or classification in a blinded manner.

4.4.2. Secondary Efficacy Variables

- Incidence of major VTE through day 12 (REGN9933 versus enoxaparin). Major VTE includes: proximal DVT; confirmed symptomatic DVT of either leg; confirmed fatal or nonfatal PE including unexplained death for which PE cannot be ruled out
- Incidence of DVT as measured by venography of the operated leg on day 10 ±2 days (REGN9933 vs enoxaparin)
- Incidence of confirmed, adjudicated VTE through day 12 (enoxaparin vs apixaban)

4.4.3. Exploratory Efficacy Variables

- Incidence of confirmed VTE through day 12 (REGN9933 vs apixaban) and through the end of study
- Incidence of major VTE through the end of study

- Incidence of confirmed symptomatic DVT in either leg through day 12 or 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

4.5. Safety Variables

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

4.5.1. Adverse Events and Serious Adverse Events

AEs and serious adverse events (SAEs) will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a PT and associated primary SOC according to the latest available version of MedDRA.

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

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 (e.g., 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 (e.g., 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 as per study protocol.

An adverse event of special interest (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.

Adverse Events of Special Interest for this study are:

- Moderate or severe infusion reactions
- Moderate or severe hypersensitivity reactions potentially related to study treatment
- Moderate to severe bleeding (both spontaneous and non-spontaneous)

4.5.2. 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, CRNM bleeding and minimal bleeding through time of venography (or day 12, whichever is earlier) and through the end of study will be summarized by each treatment group.

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 extra surgical 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 (e.g., 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 (i.e., 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. Minimal bleeding will be captured separately as an exploratory endpoint.

4.5.3. Laboratory Safety Variables

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 4. Tests (Blood Chemistry, Hematology, Urinalysis, and Other Laboratory Tests) are described in protocol Section 9.2.3.7.

4.5.4. Vital Signs

The following vital signs parameters will be collected at each clinic visit from screening to end of study (EOS) or at the time of early termination (ET):

- Temperature (°C)
- Semi-recumbent blood pressure (mmHg)
- Pulse rate (beats/min)
- Respiratory rate (breaths/min)

4.5.5. ECG

A standard 12-Lead ECG will be performed at time points according to Table 3. Heart rate will be recorded from the ventricular rate and the PR, QRS, and QT (QTcB and QTcF) intervals will be recorded. The ECG strips or reports will be retained with the source.

4.6. Pharmacokinetic Variables

The Pharmacokinetic (PK) variable is the concentration of total REGN9933 in serum at scheduled time points on Table 3 and Table 4.

4.6.1. 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 3 and Table 4.

4.7. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and time-point/visit. Samples in this study will be collected at the clinical visits as specified in Table 3 and Table 4.

4.8. Pharmacodynamic and Other Biomarker Variables

Plasma for aPTT and PT biomarkers will be analyzed by a central laboratory, and they will be used for the secondary PD endpoints.

Additional PD and biomarker variables include FXI:C (a measure of FXI activity), 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 3 and Table 4.

5. STATISTICAL METHODS

Unless otherwise stated, the following conventions will be applied when presenting summary level statistics for data.

Continuous variables will be summarized within each treatment group, presenting the following descriptive statistics: the number of participants reflected in the calculation (n), average, sample standard deviation (SD), median, minimum, maximum, 1st quartile and 3rd quartile.

Categorical or ordinal data will be summarized within each treatment group by frequency (i.e. total number of observations within each level of the categorical variable in a given treatment group) and percentages. All levels of the categorical variable will be included. If there are observations where the level of the categorical variable is missing, a separate category titled "Missing" will be created. For categorical variables that are ordinal in nature, the order in which the levels of the categories are displayed will be consistent with the natural ordering of the category levels. Percentages will also be calculated for each level of the categorical variables with respect to the total sample size for the respective treatment arm.

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group based on SAF.

5.2. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The frequency and percentage of each medical history will be summarized by associated primary SOC and PT for each treatment arm on the SAF. The table will be sorted by decreasing frequency of SOC followed by PT based on the overall incidence across treatment groups.

5.3. Prior / Concomitant Medications

The prior and concomitant medication will be descriptively summarized by treatment group on the SAF, sorted by decreasing frequency of ATC Level 2 and ATC level 4 of the total group. The use of anti platelets, anticoagulants (outside of assigned treatments), and NSAIDs may be included if deemed necessary.

5.4. Subject Disposition

The following summaries of number and percentage by each treatment group and overall group will be provided:

- The number of participants screened (signed the informed consent form) and the reasons for screen failure
- The number of participants randomized (received a randomization number)
- The number of participants treated

- The total number of participants who discontinued the study treatment and the reasons for the discontinuation
- A cross-tabulation of participants by planned and actual randomization strata for quantifying the mis-stratification

5.5. Measurement of Treatment Compliance

Treatment compliance will be summarized by treatment group.

For each study arm, its compliance will be calculated as follows:

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

where the number of planned administrations by each study drug is calculated as:

- For participants assigned to the enoxaparin arm, the number of planned administrations is the number of days in the on-treatment period, which is defined as the period from the date of the first dose of study drug to the time of venography (or day 12, whichever is earlier).
- 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, which is defined as the period from the date of the first dose of study drug to the time of venography (or day 12, whichever is earlier).
- For participants assigned to the REGN9933 arm, the number of planned administrations is one.

5.6. 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 participant received enoxaparin or apixaban administrations.

5.7. Analysis of Efficacy Variables

The efficacy analyses will be performed using the mITT analysis set.

Pooling of Sites/Centers

For this multi-center study, a small number of participants are ancipated at some sites. Since these study sites may not provide appropriate information to allow the analysis, the efficacy analyses adjusted/stratified by country instead of site will be conducted.

5.7.1. Analysis of Primary Efficacy Variable

The primary analysis is to evaluate the efficacy of REGN9933 for the prevention of VTE after unilateral TKA, compared to enoxaparin. The primary efficacy variable is a binary indicator whether a particiant has an adjudicated, confirmed VTE through day 12.

For any participant *i*, let p_i denote the VTE probability, trt_i denote the treatment assignment (0: enoxaparin, 1: REGN9933, 2: apixaban) , $country_i$ denote the country indicator (1, 2, .., K), and age_grp_i be the age group indicator (0: $age < 70$ *and* 1: $age \geq 70$).

The following Bayesian logistic regression model adjusted by stratification factors (country and age group) is specified to compare the event rates of VTE among enoxaparin, REGN9933, and apixaban:

$$logit(p_i) = \beta_0 + \beta_1 * I(trt_i = 1) + \beta_2 * I(trt_i = 2) + \sum_{k=1}^{K-1} \theta_k * I(country_i = k) + \gamma * age\_grp_i$$

where β_0 is the log odds of the VTE rate from enoxaparin, β_1 is the log odds ratio of REGN9933 relative to enoxaparin, and β_2 is the log odds ratio of apixaban relative to enoxaparin after adjustment by country and age group. The benefit of the treatment effect of REGN9933 over enoxaparin is expressed in terms of the odds ratio (=e^{β_1}) that is less than 1.

A weak prior N(0,0.843) is chosen for parameters β_1 and β_2. With this weak prior, the extreme treatment difference is unlikely, i.e., the probability of the odd ratio between 0.25 and 4 is around 90%. A vague prior $N(0,10^4)$ is used for the other regression parameters.

The treatment effect will be estimated using the Markov Chain Monte Carlo (MCMC) method via PROC BGLIMM in SAS. The SAS code for implementing the Bayesian logistic regression model is provided in Appendix 11.4.1

Bayesian summary statistics (posterior mean and median, and two-sided 90% credible interval) of the treatment effect of REGN9933 vs enoxaparin (odds ratio = e^{β_1}) will be reported.

Based on the logistic regression model, the treatment effect (odds ratio = $e^{\beta_1 - \beta_2}$) of REGN9933 vs apixaban and the treatment effect (odds ratio = e^{β_2}) of apixaban vs enoxaparin will be reported. Their crediable interval such as two sided 90% credible interval will also be reported.

The probability-based quantities for the magnitude of treatment effect at thresholds of clinical interest may be provided, e.g., Prob(OR < 0.5, 0.8, 0.9, etc. | data).

5.7.2. Analysis of Secondary and Exploratory Efficacy Variables

Unless otherwise specified, categorical efficacy endpoints (defined in Section 4.4.2 and Section 4.4.3) will be analyzed by Bayesian logistic regression models in a similar manner for the primary efficacy variable on the mITT set.

Bayesian summary statistics (posterior mean and median, and two-sided 90% credible interval) of the treatment effect (odds ratio) will be reported.

For the explaratory analyses, the distribution of DVT (proximal versus distal) will be summarized descriptively for participants detected on venogram. Proximal DVT will be characterized by the size of the venous thromboembolism (VTE), while distal DVT will be summarized by the number of affected veins.

5.7.3. Sensitivity Analysis

To assess the robustness of the Bayesian model on the choice of prior distributions, sensitivity analyses will be performed and reported for these possible prior distributions for parameters β_0, β_1, and β_2 (including but not limited: N(0,1), N(0,10), N(0,100), and N(0,10^6)).

A Bayesian logistic regression model with these two covariates (country and treatment group) will be explored to assess the treatment effect conditional on country only.

To assess the sensitivity of the Bayesian logistic model, the stratified Cochran-Mantel-Haenszel (CMH) method by both country and age group will be performed. The SAS code for CMH analysis is provided in Appendix 11.4.2. The stratified CMH by country only as the stratification factor will also be explored.

5.7.4. Subgroup Efficacy Analysis

Subgroup efficacy analyses on the primary efficacy variable and secondary efficacy variables will be performed on the following subgroups:

- Gender (Male, Female)
- BMI
- Age group(<70 vs ≥ 70)
- Site
- Country
- Duration of TKA surgery

However, as such analyses may not have enough power for hypothesis tests, the analysis will be exploratory in nature.

5.7.5. Multiplicity Control

As the statistical inference for this study is to focus on estimation rather than testing a formal hypothesis and the Bayesian analysis is performed, the multiplicity adjustments of the different comparisons between groups will not be done.

5.8. Analysis of Safety Data

The safety analysis will be performed on the SAF.

5.8.1. Analysis of Adverse Events

AE incidence tables will be presented for each treatment group, including the number (n) and percentage (%) of participants experiencing an AE, where multiple instances of the same event

occur in the same participant the event will be counted only once for that participant. The denominator for computation of percentages is the number of participants in each treatment group.

Treatment Emergent Adverse Events (TEAEs) are defined as AEs with either initial onset after the first dose of study treatment or that worsen after the first dose of study treatment. The number and proportion of participants reporting TEAEs will be summarized by SOC and PT.

Overall TEAE summary

The overall summary of TEAEs will be provided with number and proportions of participants with any:

- TEAEs
- Treatment-emergent serious adverse events (TE-SAEs)
- TEAEs of special interest (TE-AESI)
- Summary of deaths

TEAE incidence

Number and proportions of participants reporting TEAEs will be summarized for the following TEAEs:

- TEAEs
  - TEAEs by primary SOC and PT
  - TEAEs by primary SOC, PT and severity
  - TEAEs related to study drug by primary SOC and PT
  - Treatment-related TEAEs by primary SOC, PT and maximum severity
  - TE-AESI by primary SOC and PT
  - TEAEs leading to permanent treatment withdrawal by primary SOC and PT
- TE-SAEs
  - TE-SAEs by SOC and PT
  - Treatment-related TE-SAEs by primary SOC and PT
- TEAEs leading to death by primary SOC and PT

5.8.2. Assessment for Bleeding

Participants will be assessed for surgical site bleeding events at time points according to Table 3. 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 3. 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 extra surgical), 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 4.5.2.

5.8.3. Analysis of Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry, hematology and urinalysis results, and will be converted to standard international units and US conventional units. Summaries of laboratory variables will include:

- Descriptive statistics of laboratory result and change from baseline by visit
- The number (n) and percentage (%) of participants with treatment-emergent PCSVs during study
- Shift tables based on baseline normal/abnormal may be used to present the results for parameters of interest

5.8.4. Analysis of Vital Signs

Summaries of vital sign variables will include:

- Descriptive statistics of vital sign variable and change from baseline by visit
- The number (n) and percentage (%) of participants with treatment-emergent PCSV, depending on data

5.8.5. Analysis of ECG

Summaries of 12-lead ECG parameters by treatment group will include:

- Each ECG parameter and change from baseline
- The number (n) and percentage (%) of participants with PCSV, depending on data
- ECG status (i.e. normal, abnormal) summarized by a shift table

5.8.6. Analysis of Pharmacokinetics 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 and total FXI over time 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.

5.8.7. Analysis of Immunogenicity Data

Immunogenicity variables described in Section 4.7 will be summarized by ADA status, ADA category and maximum titer observed in participants in the ADA analysis set. For samples confirmed as drug specific ADA positive, but found negative at the lowest titer dilution, the lowest dilution in the titer assay is imputed.

The ADA status of each participants may be classified as one of the following:

- Positive
- Pre-existing immunoreactivity: if the baseline sample is positive and all post baseline ADA titers are reported as less than 9-fold the baseline titer value.
- Negative: if all samples are found to be negative in the ADA assay.

The ADA category of each positive participants is classified as:

- Treatment-emergent ADA response: A negative results or missing result at baseline with at lease one positive post baseline result in the ADA assay.
- Treatment-boosted ADA response: A positive result at baseline in the ADA assay with at least one post baseline result ≥9-fold the baseline titer value

Maximum ADA Titer category of each participants is classified as:

- Low (titer <1,000)
- Moderate (1,000≤ titer ≤10,000)
- High (titer >10,000)

The following will be summarized by treatment group and ADA titer level:

- Number (n) and percent (%) of ADA-negative participants
- Number (n) and percent (%) of pre-existing participants
- Number (n) and percent (%) of treatment-emergent ADA positive participants
- Number (n) and percent (%) of treatment-boosted ADA positive participants

5.8.8. Association of Immunogenicity with Exposure, Safety and Efficacy

Immunogenicity and Exposure
Potential association between immunogenicity and systemic exposure to REGN9933 will be explored by treatment groups. Plots of individual REGN9933 concentration time profiles may be provided to examine the potential impact of ADA category, maximum titer category.

Immunogenicity and Safety and Efficacy
Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Infusion reactions
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylactic Reaction [Narrow])

Potential association between immunogenicity variables and efficacy endpoints may be explored (e.g., scatter plot or spaghetti plot).

The safety and efficacy analyses mentioned above will be conducted using the following categories:

- ADA Positive
- Treatment-emergent
- Treatment-boosted
- Maximum post-baseline titer category in ADA positive participants

The association of immunogenicity with exposure, safety and efficacy analysis will be performed and reported separately.

5.8.9. Analysis of Pharmacodynamic and Exploratory Biomarker Data

The analysis of Pharmacodynamic and Biomarker will be performed in the PD analysis set using all observed data.

For biomarkers including aPTT, PT, 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, percent change, and/or fold change from baseline to each scheduled assessment time will be summarized by treatment with descriptive statistics if deemed appropriate.

TGA for extrinsic and intrinsic pathways will be analyzed separately.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the baseline measurement for all measurements will be the latest available valid measurement taken prior to the administration of study drug. If any randomized participants are not treated, the baseline will be the last value on or prior to the randomization. The following rules specify the determination by both date/time information:

1. For the AE, lab (including biomarker), drug concentration and ADA data, both date and time of the measurement will be used to determine baseline by comparing with the first infusion date and time.
2. For other data except AE, lab (including biomarker), drug concentration or ADA, only date of measurement will be used to determine baseline by comparing with the first infusion date.

For the rescreened participants, all data from the same participant will be used to derive baseline regardless if the data is from the screen- failure subject ID or enrolled subject ID.

6.2. General Data Handling Conventions

For the laboratory safety variables and biomarker data, if the data below the lower limit of quantification (LLOQ) / limit of linearity, half of the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ) / limit of linearity, the upper limit value (i.e., ULOQ) will be used for quantitative analyses.

6.3. Data Handling Convention for Missing Data

Missing data will not be imputed in listing. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Adverse event

If the intensity of a TEAE is missing, it will be classified as “severe” in the frequency tables by intensity of TEAEs. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as related to the investigational product.

Missing date

Every effort will be made to collect the start dates of all AEs and concomitant medications/procedures. However, in the case the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the first dose of study medication, except if an incomplete date (e.g., month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the first dose of study medication date, then the start date of the first dose will be imputed, otherwise, the missing day or month by the first day or the first month will be imputed.

Potentially Clinically Significant Value (PCSV)

If a participant has a missing baseline value, this participant will be grouped in the category "normal/missing at baseline".

For PCSVs with 2 conditions, one based on a change from baseline value and the other on a threshold value or a normal range, with the first condition being missing, the PCSV will be based only on the second condition.

For a PCSV defined on a threshold and/or a normal range, this PCSV will be derived using this threshold if the normal range is missing; e.g., for eosinophils the PCSV is >0.5 giga/L or >ULN if ULN≥0.5 giga/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSVs.

For laboratory results below the quantifiable LOQ, half of the LOQ will be imputed for calculating the descriptive summary.

No imputations for missing laboratory data, ECG data, vital sign data, or physical examination data will be made.

6.4. Visit Windows

Data analyzed by-visit-analysis (including efficacy, laboratory data, visit sign, ECG) will be summarized by the study scheduled visits described Appendix 11.2, "Schedule of Event". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits and early termination (ET) visit have the potential to be summarized. No analysis visit windows will be applied for the study scheduled visits. The visit windows are constructed using ranges applied to the number of days in study (study days) when the measure is collected.

The following analysis visit windows will be used to map the unscheduled visits and ET visits, based on the study day:

Visit	Target Day (TD)	Analysis Time Window Based on Study Day
Visit 1 (Screening)	-30 to -1	-29 to -2
Visit 2 (Baseline)	1	1
Visit 3	5	[4, 6]
Visit 4	10	[8, 12]
Visit 5	30	[27, 33]

Visit 6 (End of Study)	75	[70, 80]

Notes:

1. Additional visits will be created as needed depending on the aPTT results per cohort
2. End of Study visit will be mapped according to its actual day

In general, the following order will be used to select the record for analysis at give visit:

1. Scheduled visit
2. Early termination (ET) or end of study (EOS), whichever comes first if scheduled visit is not available
3. Unscheduled visit if both scheduled visit and ET/EOT/EOS are not available

For multiple measurements of the same test in the same window, the following rules will be used to select the analysis value:

1. If multiple valid values of a variable within an analysis visit window, the closest from the target study day will be selected.
2. If the difference is a tie, the value after the target study day will be used.
3. If multiple available values of a variable exist within a same day, then the first value of the day will be selected

7. INTERIM ANALYSIS

An informal IA will be conducted by the sponsor when there are approximately 50 participants per arm who have evaluable primary endpoints (i.e. adjudicated, evaluable venography or confirmed VTE through day 12).

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

The IA may include safety, efficacy and demographic and other baseline charateristics variables.

8. STUDY COMMITTEES

8.1. 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 will perform regular safety data assessment of study participants and provide recommendations to Regeneron regarding the safety and the welfare of the participants exposed to REGN9933.

Detailed information regarding the DMC procedures are provided in a separate DMC charter.

8.2. Steering Committee

The Steering Committee is composed 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 are provided in a separate Steering Committee charter.

8.3. Adjudication Committee

The AC is 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 are explained in a separate Adjudication Committee charter.

9. SOFTWARE

All analyses will be done using SAS Version 9.4 or higher, and R version 3.5.0 or higher.

10. REFERENCES

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Schulman S, Angerås U, Bergqvist D, Eriksson B, Lassen MR,Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 2010; 8(1):202-204.

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Weitz JI, Bauersachs R, Becker B, Berkowitz SD, Freitas MCS, Lassen MR, et al. Effect of Osocimab in Preventing Venous Thromboembolism Among Patients Undergoing Knee Arthroplasty: The FOXTROT Randomized Clinical Trial. Jama 2020; 323(2):130-139.

11. APPENDIX

11.1. Summary of Statistical Analyses

Table 1: Efficacy/PD Analyses

Endpoint	Analysis Populations	Primary Statistical Method/Analysis	Sensitivity Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint					
Proportions of participants with adjudicated, confirmed VTE through day 12	*mITT*	*Bayesian logistic regression*	*Stratified CMH analysis*	*Yes*	*No*
Secondary/PD Endpoints					
Secondary efficacy endpoints	*mITT*	*Bayesian logistic regression*	*Stratified CMH analysis*	*Yes*	*No*
aPTT, PT	*PDAS*	*Descriptive Statistics*	*No*	*No*	*No*
FXI:C, TGA	*PDAS*	*Descriptive Statistics*	*No*	*No*	*No*

Table 2: Safety Analyses

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive Statistics	No	No	No
Laboratory Measures	SAF	Descriptive Statistics	No	No	No
Vital Signs	SAF	Descriptive Statistics	No	No	No
ECG	SAF	Descriptive Statistics	No	No	No

11.2. Schedule of Time and Events

Table 3: 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]			
Participant 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					
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

	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**
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

11.2.1. Footnotes for the 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 protocol 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 4 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 4.
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.

Table 4: 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

11.2.2. Footnotes for 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.

11.3. Criteria for Potentially Clinically Significant Values (PCSV)

Parameter	PCSV Criteria	Comments and References
Clinical Chemistry		
ALT*	>3 ULN and baseline ≤1 ULN* >6 ULN and baseline ≤3 ULN	Enzyme activity must be expressed in ULN, not in IU/L. U. S. Food and Drug Administration. Center for Drug Evaluation and Research. (2009). *Drug-Induced Liver Injury: Premarketing Clinical Evaluation* Each category is calculated independently.
AST*	>3 ULN and baseline ≤1 ULN* >6 ULN and baseline ≤3 ULN	Enzyme activity must be expressed in ULN, not in IU/L. U. S. Food and Drug Administration. Center for Drug Evaluation and Research. (2009). *Drug-Induced Liver Injury: Premarketing Clinical Evaluation* Each category is calculated independently. * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution across the different PCSV levels, additional shift table on ≤3, >3 to ≤5, > 5 to ≤10, >10 to ≤20, and > 20 category for baseline vs. post baseline may be provided
Alkaline Phosphatase	>2.5 ULN and baseline ≤1.5 ULN	Enzyme activity must be expressed in ULN, not in IU/L. U. S. Food and Drug Administration. Center for Drug Evaluation and Research. (2009). *Drug-Induced Liver Injury: Premarketing Clinical Evaluation*
Total Bilirubin*	>2 ULN and baseline ≤1.5 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. U. S. Food and Drug Administration. Center for Drug Evaluation and Research. (2009). *Drug-Induced Liver Injury: Premarketing Clinical Evaluation* * At least one level is required, multiple levels are optional for phase 2/3 studies. If it is desirable to get the distribution of significant level, additional shift table on ≤1.5, >1.5 to ≤2.0 and > 2.0 category for baseline vs. post baseline may be provided
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN, and baseline ALT ≤1 ULN **or** TBILI ≤1.5ULN	U. S. Food and Drug Administration. Center for Drug Evaluation and Research. (2009). *Drug-Induced Liver Injury: Premarketing Clinical Evaluation*

Parameter	PCSV Criteria	Comments and References
Creatinine	≥150 µmol/L (Adults) and baseline < 100 µmol/L ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994. 3 independent criteria
Blood Urea Nitrogen	≥30 mmol/L and baseline <17 mmol/L	One independent criteria
Sodium Hyponatremia Hypernatremia	≤125 mmol/L and baseline >129 mmol/L ≥160 mmol/L and baseline <155 mmol/L	Two independent criteria
Potassium Hypokalemia Hyperkalemia	<3 mmol/L and baseline ≥3 mmol/L ≥5.5 mmol/L and baseline <4.9 mmol/L	FDA Feb 2005. Two independent criteria
Glucose Hypoglycaemia Hyperglycaemia	≤3.9 mmol/L and <LLN and baseline >5.9 mmol/L ≥11.1 mmol/L	ADA Jan 2008.
Albumin	≤32 g/L and baseline >35 g/L	
Hematology		
WBC	<2.0 Giga/L and baseline ≥4.0 Giga/L ≥16.0 Giga/L and baseline <10 Giga/L	Increase in WBC: not relevant. *The default criteria. Summary by race (black and Non-black) are optional. To be interpreted only if no differential count available.
Neutrophils	<1.0 Giga/L and baseline ≥2 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.
Eosinophils	>1 Giga/L and baseline ≤0.4 Giga/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤10 g/L and baseline >12 g/L *Decrease from Baseline ≥30 %	Two criteria are independent. Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L). *based on expected post-operative changes

Parameter	PCSV Criteria	Comments and References
Hematocrit	≤0.32 v/v and baseline >0.38 v/v *Decrease from Baseline ≥30 %	The first criteria is the follow up value. *based on expected post-operative changes
Platelets	<50 Giga/L and baseline ≥100 Giga/L ≥700 Giga/L and baseline <400 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991. Two independent criteria
Vital signs		
HR	≤50 bpm ≥130 bpm	To be applied for all positions except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20 mmHg ≥165 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥105 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions except STANDING.
ECG		
HR	≤45 bpm ≥130 bpm	Two independent criteria and evaluate follow up values.
PR	≥220 ms	
QRS	≥120 ms	
QTc Prolonged**	Prolonged: >450 ms for male or >470 ms for female	QT correction formula to be applied is the Fridericia. *The default criteria. By gender (male and female) are optional. **QTc prolonged and ΔQTc>60 ms are the PCSV to be identified in individual subjects/patients listings.

11.4. SAS Code for Efficacy Analysis

11.4.1. SAS Code for Primary Efficacy Analysis Using Bayesian Logistic Regression

The Bayesian logistic regression model is implemented below by SAS PROC BGLIMM. The variable and dataset names are for illustration purpose and may be subject to change:

```
proc bglimm data=adeff nmc=20000        seed=205169;
    class country age_grp vte trt;
     model vte(event='yes') = trt country age_grp / dist=binary cprior=normal(input=priordata);
run;
```

11.4.2. SAS Code for Stratified CMH

The stratified CMH method is implemented by Proc Freq. The variable *event* is a binary indicator, which is used for illustration purpose only.

```
Proc freq data= adeff ;
    tables country*age_grp*trt*event/cmh commonriskdiff;
    ods output cmh=cmh;

run;
```

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