REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: 1.0

CLINICAL STUDY PROTOCOL TITLE:

A Phase 2, Multicenter, Randomized, Open-Label, Active-Control Study of REGN7508, A Factor XI Monoclonal Antibody, for Prevention of Venous Thromboembolism After Elective, Unilateral, Total Knee Arthroplasty

Compound: **REGN7508**

Protocol Number: **R7508-DVT-2360 Amendment 1**

Clinical Phase: **Phase 2**

Sponsor: **Regeneron Pharmaceuticals, Inc.**

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Version/Date: **Original Statistical Analysis Plan / 08AUG2024**

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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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
BMI	Body mass index
BUN	Blood urea nitrogen
C_{max}	Peak concentration
CRNM	Clinically relevant non-major
DOAC	Direct oral anticoagulants
DNA	Deoxyribonucleic acid
DVT	Deep venous thrombosis
ECG	Electrocardiogram
EOS	End of study
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
ISTH	International Society on Thrombosis and Hemostasis
INR	International normalized ration
IV	Intravenous
MCMC	Markov Chain Monte Carlo
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
mITT	Modified intent to treat
NSAIDS	Non-steroidal anti-inflammatory drug

OLTP	Open-label treatment period
OR	Odds ratio
OR_{RE}	the odds ratio of confirmed VTE in participants administered REGN7508 as compared to that of enoxaparin
PCSV	Potentially Clinically Significant Value
PD	Pharmacodynamic(s)
PE	Pulmonary embolism
PK	Pharmacokinetic(s)
PT	Prothrombin time
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
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
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 SAP is intended to be a comprehensive and detailed description of the statistical methods, timing of analyses and analysis presentation to be used for the study specified in protocol R7508-DVT-2360 Amendment 1 dated June 12 2024.

1.1. Study Description and Objectives

This Phase 2, multicenter, randomized, open-label, active-control study is designed to evaluate the efficacy of REGN7508 for prevention of venous thromboembolism (VTE) after unilateral total knee aethroplasty (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 REGN7508 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 (ie, major and clinically relevant non-major [CRNM] bleeding) of REGN7508 after unilateral TKA through time of venography, compared to enoxaparin
- To assess overall safety and tolerability of REGN7508 in participants undergoing TKA
- To evaluate the efficacy of REGN7508 in prevention of clinically relevant VTE, compared to enoxaparin
- To evaluate the efficacy of REGN7508 in prevention of DVT detected by venography, compared to enoxaparin
- To evaluate the pharmacokinetics (PK) of REGN7508 after single intravenous (IV) administration
- To assess pharmacodynamic (PD) effects of REGN7508 on intrinsic and extrinsic coagulation pathways (ie, activated partial thromboplastin time [aPTT], prothrombin time [PT])
- To assess immunogenicity following a single dose of REGN7508 over time

1.1.3. Exploratory Objectives

The exploratory objectives of the study are:

- Explore the efficacy of REGN7508 in prevention of VTE after unilateral TKA through the EOS, compared to enoxaparin

- Explore the efficacy of REGN7508 in prevention of symptomatic, clinical thrombosis, compared to enoxaparin
- Explore the extent of DVT burden on venography in participants receiving REGN7508 compared to enoxaparin
- Explore the bleeding risk (ie, major bleeds and CRNM) of REGN7508 after unilateral TKA through EOS compared to enoxaparin
- Explore the occurrence of minor bleeding compared to enoxaparin
- Explore biomarkers related to FXI inhibition by REGN7508
- Expand molecular understanding of venous thromboembolism, and related diseases
- Explore relationships between PK, biomarkers of anticoagulant activity, and efficacy
- To study REGN7508 mechanism of action in 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 collected from consented participants

1.2. Statistical Hypothesis

The statistical hypothesis is odds ratio (OR) of confirmed VTE in participants administered REGN7508 as compared to that of enoxaparin (OR_{RE}) is less than one, i.e. the the incidence of confirmed VTE is lower in the REGN7508 arm compared to the enoxaparin arm.

1.3. Interim Analysis (IA)

For internal decision-making purposes, an analysis of evaluable drug concentration data and pharmacodynamic data will be conducted by the sponsor when there are at least 24 participants in the REGN7508 arm who complete visit 4 (i.e., day 10 ± 2).

Additional interim analyses may be conducted either to address requests from regulatory authorities or for internal decision-making purposes. The analyses will not be used to make any decisions regarding the conduct of this study, eg, to stop the study. Investigators and participants will not be informed about the results of the analyses, unless required by law.

1.4. Modifications from the Statistical Section in the Final Protocol

The wording regarding the time frame of the efficacy endpoints, as outlined in section 7.1, has been slightly changed from “through day 12” to “through visit 4”.

For example, the primary endpoint is now defined as

- This is a composite endpoint of confirmed asymptomatic DVT, confirmed symptomatic VTE (symptomatic DVT of either leg as well as confirmed fatal or nonfatal PE), and unexplained death for which PE cannot be ruled out through visit 4.

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 period (OLTP) and follow-up period with REGN7508 or enoxaparin. Participants who are at least 50 years of age and undergoing elective, unilateral TKA will be randomized after surgery to 1 of 2 treatment arms – REGN7508 or enoxaparin – in a ratio of 2:1, 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 the REGN7508 arm and 60 participants in the comparator arm, for a total of up to approximately 180 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 competion of surgery to treatment in one of the following groups:

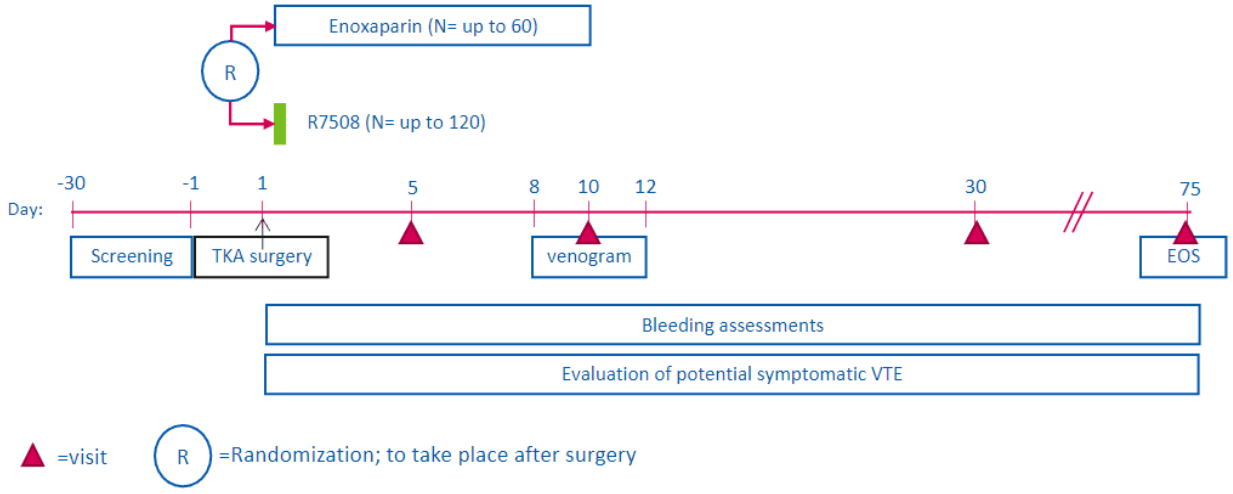
- REGN7508 250 mg IV, once
- Enoxaparin 40 mg SC, daily

Dosing with REGN7508 will occur 12 to 24 hours after the end of surgery.

Dosing with enoxaparin 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) participants.

Below is the study follow 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 180 participants will be randomized in a 2:1 allocation ratio to REGN7508 and enoxaparin.

The sample size was determined through Bayesian approach. 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, i.e. the probability that OR is between 0.25 and 4 is 90%.

The probability of any beneficial effect of REGN7508 over enoxaparin can be assessed by the posterior distribution of the odds ratio comparing REGN7508 to enoxaparin of confirmed VTE. A beneficial effect is where $OR_{RE} < 1$, and thus the study will estimate Prob(OR_{RE} <1 | data).

The sample size of 120 participants per arm was determined through 10000 trial simulations, assuming confirmed VTE event rates of 13% for REGN7508 and 22.4% for enoxaparin (Verhamme, 2021) (Weitz, 2020). Out of the 10000 simulated trials, 75% of the simulated trials with Prob(OR_{RE} <1 | data) >0.95 have the sample size of 120 or less.

For the active control arm (enoxaparin), the data from the previous trial (ROXI-VTE I) will be incorporated through a Bayesian framework using the power prior approach (Chen, 2000) (Ibrahim, 2015). The weight of the prior data can be adjusted using a power parameter, which scales from 0 to 1, according to the similarity of the prior and current trial data. The power parameter is chosen to be 0.5, which is equivalent to discounting control (enoxaparin) arm in the present study by half compared to the size of the enoxaparin arm in ROXI-VTE I and hence 60 participants will be enrolled in the enoxaparin arm in this study.

3. ANALYSIS SETS

The following defines the set(s) of participants whose data will be used for statistical analysis. All analysis sets are defind based on the treatment received (as treated). Participants who receive both REGN7508 and enoxaparin will be included in the REGN7508 group.

3.1. Efficacy Analysis Set (mITT)

The primary analysis will be conducted in the mITT population, consisting of randomized and treated participants that have either an evaluable venogram or a confirmed episode of venous thromboembolism.

3.2. Safety Analysis Set (SAF)

The SAF includes all randomized participants who received any study drug; Treatment compliance/ administration and all clinical safety variables will be analyzed using the SAF.

3.3. Pharmacokinetic Analysis Sets

The PK analysis population includes all participants in the REGN7508 treatment group who received study drug and who had at least one non-missing drug concentration result following the first dose of study drug.

3.4. Immunogenicity Analysis Sets

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

3.5. Pharmacodynamic Analysis Sets

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

4. GENERAL STATISTICAL ANALYSIS CONSIDERATIONS

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

Continuous variables will be summarized within each treatment group, presenting the following summary statistics: The number of observations with an available value of the variable, mean, standard deviation, median, minimum, maximum, 1st quartile and 3rd quartile.

Categorical 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). 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 group.

5. PARTICIPANT 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 and the reasons for the discontinuation

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1. Demographics

The following demographic variables will be summarized by treatment group and overall:

- 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:

- 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)

6.2. Medical History

Participant medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The frequency and percentage of each medical history will be summarized by primary SOC and PT for each treatment group, and overall based on the SAF.

7. EFFICACY/PHARMACODYNAMIC DATA

7.1. Description of Efficacy Data

7.1.1. Primary Efficacy Data

The primary efficacy variable is adjudicated, confirmed VTE as confirmed by a centralized independent AC. This is a composite endpoint of confirmed asymptomatic DVT, confirmed symptomatic VTE (symptomatic DVT of either leg as well as confirmed fatal or nonfatal PE), and unexplained death for which PE cannot be ruled out through visit 4.

7.1.2. Secondary Efficacy Data

The secondary efficacy endpoints are:

- Incidence of major VTE through visit 4. Major VTE includes: proximal DVT; confirmed symptomatic DVT of either leg or 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 visit 4

7.1.3. Exploratory Efficacy Data

The exploratory efficacy endpoints are:

- Incidence of major VTE through the end of study
- Incidence of confirmed symptomatic DVT in either leg through visit 4 and through the end of the study
- Incidence of confirmed PE through visit 4 and through the end of study
- Incidence of fatal PE, which includes sudden death for which PE cannot be ruled out, through visit 4 and through the end of study
- 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

7.2. Analysis of Efficacy

7.2.1. Analysis of Primary Endpoints

For any participant i, let p_i denote the VTE probability, trt_i denote the treatment assignment (0: pooled enoxaparin, 1: REGN7508) , $country_i$ 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 factors (country and age group) is specified to compare the event rates of VTE among enoxaparin and REGN7508:

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

where β_0 is the log odds of the VTE rate from the enoxaparin arm, β_1 is the log odds ratio of REGN7508 relative to enoxaparin after adjustment by country and age group. The benefit of the treatment effect of REGN7508 over enoxaparin is expressed in terms of the odds ratio (=e^{β_1}) that is less than 1.

For the active control arm (enoxaparin), the data from the previous trial (ROXI-VTE I) will be incorporated through a Bayesian framework using the power prior approach (Chen, 2000) (Ibrahim, 2015).

Let the data for the current study be denoted by $\boldsymbol{D}$ and the corresponding likelihood function be denoted as $L(\boldsymbol{\Phi}|\boldsymbol{D})$ where $\boldsymbol{\Phi} = (\beta_0, \beta_1, \theta_1, \ldots, \theta_{K-1}, \gamma)$ is the vector of parameters of interest. Suppose we have the historical enoxaparin data $\boldsymbol{D_0}$ from ROXI-VTE I, and let $L(\boldsymbol{\Phi}|\boldsymbol{D_0})$ denote the likelihood function for the historical enoxaparin data $\boldsymbol{D_0}$. Here, $L(\boldsymbol{\Phi}|\boldsymbol{D})$ and $L(\boldsymbol{\Phi}|\boldsymbol{D_0})$ are general likelihood functions for the aforementioned logistic regression model. With the power prior, the corresponding posterior distribution of $\boldsymbol{\Phi}$ is given by

$$\pi(\boldsymbol{\Phi}|\mathbf{D}, \boldsymbol{D_0}, \boldsymbol{\alpha_0}) \propto L(\boldsymbol{\Phi}|\boldsymbol{D})\boldsymbol{L}(\boldsymbol{\Phi}|\boldsymbol{D_0})^{\alpha_0}\pi_0(\boldsymbol{\Phi}).$$

where α_0 scales from 0 to 1 and $\pi_0(\boldsymbol{\Phi})$ is the initial prior for the parameters $\boldsymbol{\Phi}$. According to the similarity between the prior and current trials, the power parameter α_0 is chosen to be 0.5. This means that the control (enoxaparin) arm data from the ROXI-VTE I study is discounted by half when incorporated into the present study.

A weak prior N(0,0.843) is chosen for parameter β_1. 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 other regression parameters.

The treatment effect will be estimated using the Markov Chain Monte Carlo (MCMC) method.

Bayesian summary statistics (posterior mean and median, and two-sided 90% credible interval) of the treatment effect of REGN7508 vs enoxaparin (odds ratio = e^{β_1}) will be reported.

REGN7508 is considered superior to enoxaparin if Prob(OR < 1 | data) >0.95.

7.2.1.1. Sensitivity Analysis

Sensitivity analysis will be performed with $\alpha_0 = 0$, which indicates that the analysis will only use data from the current study.

7.2.1.2. Supplemental Analyses

The probability-based quantity for the magnitude of treatment effect at a threshold of 1.6 (i.e., Prob(OR < 1.6 | data)) will also be calculated to perform a noninferiority analysis.

For the selection of the noninferiority margin:

- An event rate of 48.3% was assumed for the placebo (Fuji, 2010)
- An event rate of 22.4% was assumed for the enoxaparin arm (Verhamme, 2021) (Weitz, 2020)

Therefore, a margin of 8.6% rate difference implies retention of about 66.7% (i.e., two-thirds) of the treatment effect of enoxaparin. The corresponding noninferiority margin on OR was calculated to be 1.6 (REGN7508: 31.0% vs. enoxaparin: 22.4%). REGN7508 is considered noninferior to enoxaparin if Prob(OR < 1.6 | data) >0.95.

The difference in event rates between the REGN7508 and enoxaparin arms in this study will be calculated using the Mantel-Haenszel test adjusted for country and age group.

7.2.1.3. Subgroup Analyses

Subgroup efficacy analyses on the primary efficacy variable will be performed on the following subgroups based on Bayesian logistic regression models.

- Gender (Male, Female)
- BMI (< 25 vs ≥ 25)
- Age group (<70 vs ≥70)
- Country
- Duration of TKA surgery (< 1 hour vs ≥ 1 to < 2 hours vs ≥ 2 hours)

Posterior mean and the 90% CI of the odds ratio in subgroups of paticipants will be presented in forest plots.

7.2.2. Analyses of Secondary and Exploratory Endpoints

Unless otherwise specified, secondary efficacy endpoints (defined in Section 7.1.2) will be analyzed by Bayesian logistic regression models in a similar manner as the primary efficacy endpoint based on the mITT set.

Exploratory endpoints will be summarized descriptively. 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.

8. HYPOTHESIS TESTING METHODS AND MULTIPLICITY CONTROL

The efficacy analyses for comparisons of REGN7508 and enoxaparin will be evaluated by using a Bayesian approach (e.g. the 90% credible interval will be estimated).

No formal hypothesis test will be performed.

9. SUMMARY OF EXPOSURE DATA

9.1. Investigation Study Drug Exposure and Compliance

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

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

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 REGN7508 arm, the number of planned adminitrations is 1.
- 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).

9.2. Prior and Concomitant Medications

Any treatment administered from the time of informed consent to the final study will be recorded. This includes medications that were started before the study and are ongoing during the study. Medications will be coded using WHO Drug Dictionary (WHODRUG).

Prior medications: medications taken prior to administration of the first dose of study drug.

Concomitant medications (CM): medications taken following the first dose of study drug through the EOS visit. This includes medications that were started before the study and are ongoing during the study.

Number and percentage of participants taking prior/concomitant medications, prohibited medications and rescue medications will be summarized for each treatment group, based on SAF, by ATC Level 2 and ATC Level 4, sorted by decreasing frequency of ATC Level 2 and ATC Level 4 in the overall group. Participants will be counted only once in each medication class linked to the medication.

9.2.1. Prohibited Medications

Administration of enoxaparin prior to TKA surgery is prohibited (see protocol Section 6.2.2 Exclusion criterion 10).

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

For participants assigned to the REGN7508 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.

9.2.2. Rescue Medication

Rescue medication during the study is defined in protocol section 7.2.

9.3. Prior and Concomitant Procedures

Procedures are recorded from the day of informed consent until the EOS visit and all procedures are coded using the MedDRA. The prior and concomitant procedures are defined as below:

Prior procedures: procedures performed prior to administration of the first dose of study drug.

Concomitant procedures (CPs) for the whole study: procedures performed following the first dose of study drug through the EOS visit.

Number and proportion of participants undergoing prior/concomitant procedures will be summarized for each treatment group, based on SAF, by SOC and PT, and sorted by decreasing frequency of SOC and PT in the overall group.

10. ANALYSIS OF SAFETY DATA

The safety analyses will be conducted using the SAF. No formal statistical testing of safety endpoints will be conducted.

10.1. Adverse Events

All new or worsening adverse events (AEs) occurring between signing of the ICF and the end of the study will be recorded and coded using the MedDRA.

AE summaries will be presented for TEAEs. These 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 till the end of study.

Adverse events will be summarized with incidence tables. Adverse event incidence tables will present the number (n) and percentage (%) of participants experiencing an AE within each treatment arm, sorted by decreasing frequency of SOC and PT for the total group. Multiple occurrences of the same event in a participant will only be counted once in the summary. For tables showing AE severity, in instances where a participant has multiple occurrences of the same PT or SOC, only the worst severity will be counted in the summary.

The following summaries for TEAEs will be presented:

- TEAEs by primary SOC and PT
- TEAEs by primary SOC, PT and severity
- TEAEs related to study drug by primary SOC and PT
- TE-AESI by primary SOC and PT
- TE-SAEs by primary SOC and PT
- TEAEs leading to study discontinuation by primary SOC and PT
- TEAEs leading to death by primary SOC and PT

10.1.1. Assessment for Bleeding

The incidence tables for adjudicated major bleeding and clinically relevant non-major bleeding will present the number (n) and percentage (%) of participants experiencing a bleeding event within each treatment arm. Major bleeding and clinically relevant non-major bleeding are defined in protocol section 4.3.1.

Adjudicated minor bleeding will be summarized separately in a similar manner.

10.2. Laboratory Parameters

Laboratory measurements will be converted to values in standard international (SI) 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. Participant laboratory parameter measurements will be evaluated by PCSV criteria,

specifically identifying participants with at least one post-baseline measurement that meets the PCSV criteria (Section 14.3). Participants meeting the PCSV criteria will be summarized by participant count (and percent) for a post-baseline PCSV measurement by treatment group, regardless of baseline PCSV status. When the PCSV definition involves a change from baseline value, participants must have a baseline value to be included in the summaries. All measurements collected during the study including values from unscheduled visits will be used in the PCSV analyses.

10.3. 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 for participants who did not meet PCSV criterion at the baseline

10.4. Immunogenicity Data

10.4.1. Immunogenicity Variables

The immunogenicity variables include ADA status, titer, and time point/visit. Sample in this study will be collected at the clinic visits specified in Section 14.2 .

10.4.2. Analysis of Immunogenicity Data

10.4.2.1. Analysis of ADA Data

The immunogenicity variables described in Section 10.4.1 will be summarized by ADA status, ADA category and maximum titer category 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

The maximum titer category of each participant 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 participant
- Number (n) and percent (%) of pre-existing participant
- Number (n) and percent (%) of treatment-emergent ADA positive participant
- Number (n) and percent (%) of treatment-boosted ADA positive participant

Listing of all ADA titer levels will be provided for participants with pre-existing, treatment-emergent and treatment-boosted ADA response.

10.4.3. Association of Immunogenicity with Exposure, Safety and Efficacy

10.4.3.1. Immunogenicity and Exposure

Potential association between immunogenicity variables and systemic exposure to REGN7508 will be explored by treatment groups. Plots of individual REGN7508 concentration time profiles may be provided to examine the potential impact of ADA category, maximum titer category on these profiles.

10.4.3.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables and safety may be explored with a primary focus on the following safety events

- 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 associateion of immunogenicity with exposure, safety and efficacy analysis will be performed and reported separately.

10.5. Pharmacokinetic Data

The Pharmacokinetic (PK) variable is the concentration of total REGN7508 in serum at scheduled time points on Table 2 and Table 3.

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.

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

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

The concentrations of total REGN7508 and total FXI over time will be summarized using descriptive statistics within the REGN7508 group to estimate exposures.

This descriptive statistical assessment will include the geometric means and ratios of the geometric means for selected PK parameters, as deemed appropriate.

10.6. 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.

The analysis of pharmacodynamic and biomarker variables will be performed in the PD analysis set using all observed data.

Biomarkers including aPTT, PT, FXI:C and thrombin generation (following intrinsic and extrinsic pathway activation) measured at baseline and post-treatment will be summarized over time. Change, percent change, and fold change from baseline to each scheduled assessment time will be summarized by treatment with descriptive statistics.

TGA for extrinsic and intrinsic pathways will be analyzed separately. Analysis of TGA will not be included in CSR.

11. DATA CONVENTIONS

11.1. 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. For variables with valid measurements taken both pre-operatively and post-operatively, but prior to the administration of the study drug, the post-operatively taken measurement will be used as the baseline. 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:

- 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.
- 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 participant ID or enrolled participant ID.

11.2. Data Convention

- If the date of interest occurs on or after the first dose/randomization date, the study day will be calculated as (date of interest – date of the first dose/randomization) + 1.
- If the date of interest occurs prior to the first dose/randomization date, the study day will be calculated as (date of interest – date of the first dose/randomization).
- For categorical variables, participants with missing data will not be included in calculations of percentages unless otherwise specified. When relevant, the number of participants with missing data will be presented.
- Percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form xx (xx.x%).
- Change from baseline will be calculated as a post-baseline value minus the baseline value.
- All laboratory data will be reported using standard international units
- All analysis and summary tables will include the analysis population sample size in the column headings.
- 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.

11.3. Data for Non-Efficacy Endpoints

Adverse events

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.

Adverse event start date

If AE start day is missing, and AE start month and year are not missing: If AE start year is the same as first dose year and the AE start month is the same as the first dose month, then impute AE start day using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Otherwise impute the AE start day using the first day of the month. If this leads to a date before informed consent, the informed consent date will be used.

If AE start month is missing, and AE start year is not missing: If AE start year is less than the first dose year, use the informed consent day and month. If AE start year is equal to the first dose year, use the first dose day and month. If this leads to a date after the AE end date, use AE end date instead. If AE start year is after the first dose year, use 01 January.

If AE start year is missing: Impute AE start date using the day of first dose. If this leads to a date after the AE end date, use AE end date instead.

Adverse event end date

The general recommendation is not to impute AE end date. However, since AE end date will be used for the imputation of AE start date, in order to carry through the logic for programming, the following intermediate step will be used. Afterwards, only the original character/numeric date recorded in CRF will be kept in the final analysis dataset.

If AE end day is missing, and AE end month and year are not missing: Impute AE end date using the last day of the month. If this leads to a date after end of study follow up date, use the end of study date instead.

If AE end month is missing, and AE end year is not missing: Impute AE end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the end of study date instead.

If AE end year is missing: Impute AE end date using the end of study date.

Medication missing/partial dates

For the tabulation of prior and concomitant medication, partially missing start dates of the medication will be imputed using the same rules as for AEs.

Procedures

For the tabulation of prior and concomitant procedures, partially missing start dates of the medication will be imputed using the same rules as for AEs.

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.

11.4. Assignment of Data to Visit Windows and Unscheduled Assessments

Data analyzed by-visit-analysis (including efficacy, laboratory data, vital signs) will be summarized by the study scheduled visits described in Appendix 14.2, "Schedule of Time and Events". 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 from SOE	Target Study Day	Assessment for symptomatic VTE, Vital signs, PK, Biomarkers*	ADA	Lab (Excluding Urinalysis)**	Urinalysis	Serum/Plasma for exploratory research
Visit 1 (Screening)	-30 to -1	<1	<1	<1	<1	
Visit 2 (Baseline)	1	1	1	1		1
Visit 3	5	[2, 7]				[2, 17]
Visit 4	10	[8, 20]		[2, 42]		
Visit 5	30	[21, 52]				[18, 52]
Visit 6 (EOS)	75	≥ 53	≥ 2	≥ 43	≥ 1	≥ 53

* Plasma for aPTT, PT (central lab), Plasma for FXI activity (FXI:C) and TGA, Immunoglobulin G
** Hematology, Blood chemistry, Coagulation panel
Note that both scheduled and unscheduled measurements will be considered for determining abnormal/PCSV values for laboratory, vital signs as well as the baseline values.

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/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

12. TECHNICAL DETAILS PERTAINING TO INTERIM ANALYSIS

Not applicable

13. REFERENCES

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14. APPENDIX

14.1. Summary of Statistical Analyses

Table 1: Efficacy Analysis

Endpoint	Analysis Populations	Primary Statistical Method/ Analysis	Sentivity Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint					
Proportions of participants with adjudicated, confirmed VTE through visit 4	*mITT*	*Bayesian logistic regression with power prior to incorporate enoxaparin data from ROXI-I study*	*Bayesian logistic regression using current study only*	*Yes Subgroups: age, gender, BMI, Country, Duration of TKA surgery*	*Noninferiority analysis; Mantel-Haenszel test*
Secondary Endpoints					
Secondary efficacy endpoints	*mITT*	*Bayesian logistic regression with power prior to incorporate enoxaparin data from ROXI-I study*	*Bayesian logistic regression using current study only*	*No*	*No*
aPTT, PT	*PDAS*	*Descriptive Statistics*	*No*	*No*	*No*
FXI:C, TGA	*PDAS*	*Descriptive Statistics*	*No*	*No*	*No*

14.2. Schedule of Time and Events

Table 2: Schedule of Events

	Screening	On-treatment			Follow-up	
Study Procedure	**Visit 1**	**Baseline Visit 2**	**Visit 3[1,2]**	**Visit 4[1]**	**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	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					
TKA		X				
Randomization		X[4]				
Treatment:						
Administer REGN7508		X[5]				
Administer enoxaparin			X[6]			
Participant diary (for self-administration of enoxaparin)			X			
Efficacy:						
Venography of the operated leg				X		
Assessment for symptomatic VTE[7]		X	X	X	X	X
Safety:						
Height	X					

	Screening	On-treatment			Follow-up	
Study Procedure	**Visit 1**	**Baseline Visit 2**	**Visit 3[1,2]**	**Visit 4[1]**	**Visit 5**	**End of Study/ Visit 6**
Day	**-30 to 1**	**1**	**5**	**10**	**30**	**75**
Window (day)			**±1**	**±2**	**±3**	**±5**
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
Coagulation panel	X	X[8]		X		X
Urinalysis	X					X
Pharmacokinetics and Immunogenicity Sampling						
Drug concentration sample (REGN7508)		X[8]	X	X	X	X
ADA (REGN7508)		X[9]				X
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
Immunoglobulin G		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						

	Screening	On-treatment			Follow-up	
Study Procedure	**Visit 1**	**Baseline Visit 2**	**Visit 3[1,2]**	**Visit 4[1]**	**Visit 5**	**End of Study/ Visit 6**
Day	**-30 to 1**	**1**	**5**	**10**	**30**	**75**
Window (day)			**±1**	**±2**	**±3**	**±5**
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

14.2.1. Footnotes for 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; vital signs 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 8.2.2.2 in protocol. 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 substudy ICF (DNA analysis) musty 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 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	**Postdosing** REGN7508 only: as close as possible to 1 hour postdose
Laboratory Testing			
Hematology	X[1]		
Blood chemistry	X[1]		
Coagulation panel	X[1]		
Urinalysis	X[1]		
Pharmacokinetics and Immunogenicity Sampling			
Drug concentration sample (REGN7508)		X[2]	X[2]
ADA (REGN7508)		X[2]	
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]
Immunoglobulin G	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; PICC: peripherally inserted central catheter; PT: prothrombin time; TGA: thrombin generation assay; WOCBP: women of childbearing potential

14.2.2. Footnotes for Table 3 Schedule of Events: Visit 2 Timing of Assessments

1. Samples may be collected up to 24 hours prior to surgery. Samples to be collected in both treatment groups.

   Note: If screening is performed within 24 hours of TKA then the same set of screening laboratory samples can be used for screening and baseline

2. Samples to be collected in REGN7508 group only.
3. Samples to be collected in both treatment groups.

14.3. 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.

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