Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

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Milvexian for Prevention of Venous Thromboembolism

This supplement contains:

A: Protocols

1. The original protocol version 1, Date: 11 December 2018
2. Final version of the protocol- Including amendment 1 : 10 September 2019
3. Summary of changes
4. Country specific changes for Japan
    - 24 July 2019
    - 19 September 2019

B: Statistical analysis plan

1. Version 1 (final version), Date: 26 September 2019

Janssen Research & Development *

Clinical Protocol

Protocol Title

A Randomized, Open-Label, Study Drug-Dose Blind, Multicenter Study to Evaluate the Efficacy and Safety of JNJ-70033093 (BMS-986177), an Oral Factor XIa Inhibitor, Versus Subcutaneous Enoxaparin in Subjects Undergoing Elective Total Knee Replacement Surgery

Short Title

A Randomized Study to Evaluate the Safety and Efficacy of Oral JNJ-70033093 Versus Enoxaparin in Subjects Undergoing Elective Total Knee Replacement

Protocol 70033093THR2001; Phase 2

JNJ-70033093

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BMS-986177 is being codeveloped under a collaboration agreement between Bristol-Myers Squibb Company (BMS) and Janssen Pharmaceuticals, Inc. (Janssen).

US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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EDMS number: EDMS-ERI-172187276, 1.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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1.1. Synopsis

A Randomized, Open-Label, Study Drug-Dose Blind, Multicenter Study to Evaluate the Efficacy and Safety of JNJ-70033093 (BMS-986177), an Oral Factor XIa Inhibitor, Versus Subcutaneous Enoxaparin in Subjects Undergoing Elective Total Knee Replacement Surgery

JNJ-70033093 (Bristol-Meyers Squibb Company [BMS]-986177) is a small-molecule therapeutic agent that binds and inhibits the activated form of human coagulation Factor XIa (FXIa) with high affinity and selectivity. It is being codeveloped under a collaboration agreement between BMS and its global affiliates and Janssen Pharmaceutical Research and Development, LLC. JNJ-70033093 is being developed as an orally administered anticoagulant for the prevention and treatment of thromboembolic events (eg, venous thromboembolism [VTE]).

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To determine the efficacy of JNJ-70033093 in preventing total VTE events (proximal and/or distal DVT [asymptomatic confirmed by venography assessment or objectively confirmed symptomatic], nonfatal PE), or any death during the treatment period.	• Total VTE during the treatment period up to the time of venography as assessed by the CEC. Proof-of-efficacy is reached by either showing a positive dose response or having less than a 30% total VTE event rate in the combined dose group.
Secondary	
• To assess the dose response of JNJ-70033093 for the occurrence of the endpoint of any bleeding events during the treatment period.	• The composite endpoint of any bleeding event on treatment. Any bleeding will be defined as the composite of major, clinically relevant nonmajor bleeding events, or minimal bleeding events accessed by the CEC. Major and clinically relevant nonmajor bleeding events will be assessed according to the ISTH criteria modified for the surgical setting.
• To determine the efficacy of JNJ-70033093 in preventing total VTE events during the full study period.	• Total VTE as assessed by the CEC through Week 6.
• To assess the dose response of JNJ-70033093 for the rate of any bleeding throughout the full study period.	• Occurrence of the composite endpoint of any bleeding events, the composite endpoint of major or clinically relevant nonmajor bleeding events, and the individual components of the composite endpoint of any bleeding as assessed by the CEC through Week 6.

Objectives	Endpoints
• To assess the dose response of JNJ-70033093 for the prevention of major VTE (death, asymptomatic or symptomatic proximal DVT or PE) during the treatment period and throughout the full study period.	• Major VTE as assessed by the CEC during the treatment period and through Week 6.
• To assess the effect of individual doses of JNJ-70033093 compared with enoxaparin for both efficacy and safety endpoints.	• Total VTE and any bleeding as assessed by the CEC during the treatment period and during the full study period (6 weeks).
• To compare the effect of JNJ-70033093 with enoxaparin for the individual components of the total VTE endpoint.	• All individual components of the primary efficacy endpoint as assessed by the CEC during the treatment period and during the full study period (6 weeks).
• To assess the PK of JNJ-70033093 in men and women undergoing primary unilateral TKR surgery and the relation of these measures to efficacy and safety endpoints (eg, exposure-response analyses).	• Estimation of PK parameters and the effects of demographics and laboratory values (eg, body weight, age, gender, renal function) on the PK of JNJ-70033093. • Estimation of the relationship between JNJ-70033093 exposure levels with probability of total VTE during the treatment period up to the time of venography and the probability of the composite endpoint of major or clinically relevant nonmajor bleeding events, and the individual components of the composite endpoint of any bleeding event on treatment.
Exploratory	
• To evaluate PD to assess its relationships to PK and the relation of these measures to efficacy and safety endpoints (eg, exposure-response analyses).	• Changes in PD (aPTT, PT, FXI clotting activity, anti-FXa activity, and TGA). • Estimation of the relationship between JNJ-70033093 exposure levels with the changes in PD.
• To evaluate exploratory biomarkers to assess their relationship to the probability of total VTE during the treatment period.	• Estimation of the changes in biomarkers with the probability of total VTE during the treatment period up to the time of venography and the probability of the composite endpoint of major or clinically relevant nonmajor bleeding events, and the individual components of the composite endpoint of any bleeding event on treatment.

Objectives	Endpoints
• Explore the presence and incidence of asymptomatic MINS as it relates to total knee arthroplasty.	• The presence of an isolated elevated hs-cTnT measurement postoperatively without an alternative explanation (eg, sepsis, atrial fibrillation) in subjects with normal preoperative hs-cTnT. An incremental rise in hs-cTnT without an alternate explanation in individuals with elevated preoperative hs-cTnT.

anti-FXa=anti-Factor Xa; aPTT=activated partial thromboplastin time; CEC=Clinical Endpoint Committee; DVT=deep venous thrombosis; FXI=Factor XI; hs-cTnT=high-sensitive cardiac troponin T; ISTH=International Society on Thrombosis and Haemostasis; MINS=myocardial injury in noncardiac surgery; PD=pharmacodynamic; PE=pulmonary embolism; PK=pharmacokinetic; PT=prothrombin time; TGA=thrombin generation assay; TKR=total knee replacement; VTE=venous thromboembolism

Hypothesis

The primary hypothesis is that JNJ-70033093 reduces the risk of total VTE during the treatment period. This can be achieved by either a statistically significant dose-response trend or an event rate for the pooled doses of JNJ-70033093 that is statistically lower than 30%. The event rate of 30% is a conservative estimate of the total VTE rate in subjects given placebo.

OVERALL DESIGN

This is an open-label, study drug-dose blind, active-controlled, multicenter, dose-ranging study of JNJ-70033093 in subjects undergoing primary unilateral elective total knee replacement (TKR) surgery. The study uses the prospective, randomized, open-label, blinded endpoint (PROBE) design. Men and women who are ≥50 years of age are eligible to participate if they are considered medically stable and appropriate for anticoagulant prophylaxis as determined by the investigator.

The study will be conducted in 3 phases, which includes an up to 30-day screening phase before surgery, a 10- to 14-day postoperative dosing phase, and a 4-week ±10 days follow-up phase. Unscheduled visits may be performed at the discretion of the investigator for the assessment of any potential bleeding or efficacy endpoint events. The end of study is considered as the last visit for the last subject in the study.

An Operations Committee (OC), Steering Committee, and independent Clinical Events Committee (CEC) will be commissioned for this study. The OC will be unblinded, the Steering Committee will be blinded to the dose and frequency of JNJ-70033093, and the CEC will be blinded to both the study drug and the dose. The OC will be responsible for reviewing ongoing safety (and efficacy data) by unblinded subject treatment assignments approximately every 4 to 8 weeks.

An unblinded interim analysis is planned when approximately 400 subjects will have completed the venography or have had a symptomatic VTE event as part of an adaptive approach that will be used to guide decisions on dropping and/or adding doses of JNJ-70033093, adjusting the randomization ratio, and possibly adding preoperative dosing of JNJ-70033093. After reviewing the interim analysis data, the OC will have the option to implement or terminate 1 or more JNJ-70033093 dose regimens, including preoperative administration and the once-daily dose regimens. Additional interim analyses will be conducted, as needed, at the discretion of the OC, and the timing and the cohorts will be defined in the OC charter. These decisions will be made only after taking the safety and efficacy profiles of JNJ-70033093 into account.

NUMBER OF SUBJECTS

A target of 1,200 subjects will be randomly assigned to treatment in this study, with an option to increase the randomization target to approximately 1,500 subjects based on interim analysis results.

STUDY DRUG GROUPS AND DURATION

Up to 2 days prior to primary unilateral elective TKR surgery, eligible subjects will be randomly assigned to treatment with either JNJ-70033093 or enoxaparin. Subjects will know the treatment to which they were assigned but subjects randomly assigned to JNJ-70033093 will remain blinded to the dose and frequency (ie, BID versus once daily). Initially, all subjects randomly assigned to JNJ-70033093 will initiate the study drug the day after TKR surgery (Day 1, 0 hours). Enoxaparin may be initiated postoperatively or preoperatively at least 12 hours prior to the procedure, in accordance with local standard-of-care. Postoperative dosing of both study drugs will occur while the subject is still hospitalized, with administration beginning a minimum of 12 hours and a maximum of 24 hours after the end of TKR surgery, which is defined as the time of wound closure.

Following discharge or transfer to an alternate facility, subjects will continue to take the assigned study drug for 10- to 14-postoperative days. Unilateral venography assessment of the operated leg will be performed within 1 calendar day after the last dose of either JNJ-70033093 or enoxaparin is taken.

The total duration of participation following randomization will be approximately 6 weeks.

Each subject randomly assigned to JNJ-70033093 will take 4 capsules a day, 2 capsules in the morning and 2 capsules in the evening at approximately the same time each day, as follows:

Group A: JNJ-70033093 25 mg BID (1 capsule JNJ-70033093 25 mg and 1 placebo capsule, BID)

Group B: JNJ-70033093 50 mg BID (2 capsules JNJ-70033093 25 mg BID)

Group C: JNJ-70033093 100 mg BID (1 capsule JNJ-70033093 100 mg and 1 placebo capsule, BID)

Group D: JNJ-70033093 200 mg BID (2 capsules JNJ-70033093 100 mg BID)

Group E: JNJ-70033093 25 mg once daily (1 capsule JNJ-70033093 25 mg and 1 placebo capsules in the morning and 2 placebo capsules in the evening)

Group F: JNJ-70033093 200 mg once daily (2 capsules JNJ-70033093 100 mg in the morning and 2 placebo capsules in the evening)

Optional Group G: JNJ-70033093 (preoperatively or once daily), dose to be determined

Optional Group H: JNJ-70033093 (preoperatively or once daily), dose to be determined

No optional dose will exceed a 400-mg total daily dose.

If preoperative dose groups of JNJ-70033093 are implemented in the study then all subjects randomly assigned to JNJ-70033093 will receive a preoperative dose of JNJ-70033093 or placebo in order to preserve the blind.

Subjects randomly assigned to enoxaparin (Group I) will take a SC dose of enoxaparin 40 mg once daily, supplied as a prefilled syringe.

EFFICACY EVALUATIONS

Efficacy evaluations will include unilateral venography assessment of the operated leg and assessments of symptomatic deep vein thrombosis (DVT), pulmonary embolism (PE), or death to assess the primary, secondary, and exploratory efficacy outcomes.

PHARMACOKINETIC EVALUATIONS

Plasma samples will be analyzed to determine concentrations of JNJ-70033093 using a validated, specific, and sensitive (eg, liquid chromatography-mass spectrometry/mass spectrometry) method by or under the supervision of the sponsor. Pharmacokinetic samples will be collected from all subjects randomly assigned to JNJ-70033093.

In addition, residual plasma PK samples may be stored for future analysis of the metabolite profile, if needed.

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters (eg, apparent clearance, apparent volume of distribution) and exposure levels for exposure-response analysis of JNJ-70033093 and associated variables will be derived using population PK modeling.

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Venous blood samples will be collected for pharmacodynamic (PD) evaluation of aPTT, PT, Factor XI (FXI) clotting activity, anti-Factor Xa (anti-FXa) activity, thrombin generation assay (TGA), and biomarker evaluation (D-dimer, high-sensitive cardiac troponin T [hs-cTnT], and FXI antigen). Factor XI clotting activity will be assessed in subjects randomly assigned to JNJ-70033093 and anti-FXa activity will be assessed in subjects randomly assigned to enoxaparin. Subjects who experience a suspected bleeding event or symptomatic thrombotic event should have PD samples (except D-dimer) collected as soon as practically possible after the event occurs.

Blood samples will also be collected and a plasma sample archived for future exploratory PD research related to the safety and/or efficacy of JNJ-70033093.

SAFETY EVALUATIONS

The safety and tolerability of JNJ-70033093 will be evaluated throughout the study by the assessment of adverse events, including serious adverse events, adverse events of special interest (ie, bleeding events, liver enzyme elevations and clinical liver events, and wound or joint complications), clinical laboratory tests (ie, hematology, clinical chemistry, urinalysis), and physical examination. Safety evaluations may be performed at unscheduled timepoints, if deemed by the investigator or appropriate designee as necessary to ensure the safety of the subject. All suspected symptomatic efficacy (thrombotic) events will also be captured as adverse events of special interest.

STATISTICAL METHODS

Assuming the evaluability rate (rate of subjects with a valid assessment of potential efficacy outcome and who take a least 1 dose of study drug) is 80%, if the true underlying total VTE event rates are as projected, the study is expected to have over 99% power to declare proof-of-efficacy at a 1-sided, 5% α-level. Proof-of-efficacy is defined as either a statistically significant dose-response trend or primary endpoint event rate for the pooled BID JNJ-70033093 groups that is statistically lower than 30%. The exact power will vary because of the nature of the adaptive study design.

Comparison with enoxaparin will be based on the comparison between the highest postoperative dose with acceptable safety and enoxaparin. For example, if the highest dose for acceptable safety is 200 mg BID, the number of evaluable subjects at this dose and enoxaparin groups is expected to be 120 and 240 subjects respectively, the power to detect a statistically significantly lower total VTE event rate against enoxaparin, at 1-sided, 5% α-level, is over 90%.

The study objectives include proof-of-efficacy and estimation of dose-response relationship in total VTE. These 2 objectives will be addressed by a unified (modified) multiple comparison procedures and modeling (MCP-Mod) approach, utilizing collective data from postoperative regimens.

The intent-to-treat (ITT) population will include all randomized subjects who have signed a valid informed consent. The mITT population will be a subset of the ITT population consisting of subjects with a valid assessment of potential efficacy outcome and who take at least 1 dose of the study drug. The primary analyses of efficacy endpoints will be based on CEC-adjudicated events from the mITT population. The primary efficacy endpoint and its components will be summarized by dose and treatment group.

All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summaries, listings, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue the study drug due to an adverse event, or who experience a severe or a serious adverse event.

Adverse events of special interest are bleeding events, wound or joint complications, and liver enzyme elevations and clinical liver events. Subjects with adverse events of special interest may be counted or listed.

The safety population will be a subset of the ITT population consisting of subjects who take at least 1 dose of the study drug. The analyses of bleeding adverse events will be based on the CEC-adjudicated events; all other nonefficacy or nonbleeding adverse events will be based on investigator-reported events in the safety population.

Estimation of the dose-response relationship in any bleeding will be addressed by a unified (modified) MCP-Mod approach as with efficacy. Any bleeding, major bleeding, clinically relevant nonmajor bleeding, composite of major or clinically relevant nonmajor bleeding, and minimal bleeding will be summarized by the dose and treatment group.

Laboratory data will be summarized by type of laboratory test.

Descriptive statistics of changes from baseline will be summarized at each scheduled time point for physical examination data.

Population PK analysis of plasma concentration-time data of JNJ-70033093 will be performed using nonlinear mixed-effects modeling. Data will be listed for all subjects with available plasma concentrations per treatment group.

For each treatment group, descriptive statistics, including arithmetic mean, standard deviation (SD), coefficient of variation, median, minimum, and maximum will be calculated for all individual derived PK parameters including exposure information of JNJ-70033093. Descriptive statistics will be used to summarize JNJ-70033093 plasma concentrations at each sampling time point. Exposure-response analyses will be conducted to explore the relationship of the plasma concentration of JNJ-70033093 with efficacy and safety endpoints.

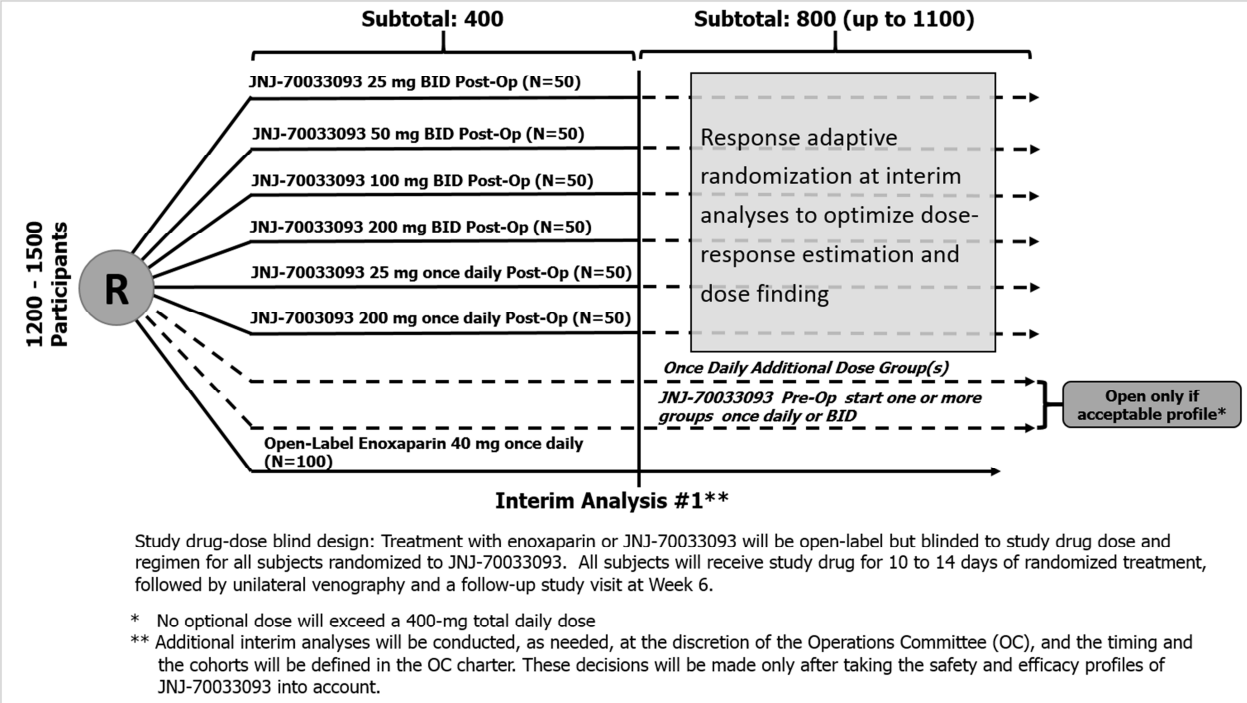
Descriptive statistics, including mean, median, SD, minimum, and maximum will be provided for the percent change from baseline of the PD (aPTT, PT, FXI clotting activity, anti-FXa activity, TGA) and biomarker (D-dimer, hs-cTnT, FXI antigen) parameters by nominal time of collection and dose and regimen level. The parameters may be statistically analyzed using mixed models.

The relationship between observed plasma concentration of JNJ-70033093 and measured PD markers will be investigated graphically. If appropriate, PK/PD exposure and response relationships may be further analyzed quantitatively.

The relationship between the plasma PK exposure levels of JNJ-70033093 derived from the population PK model will be correlated with the measured PD markers and safety/efficacy endpoints via graphical analysis.

1.2. Schema

Figure 1: Schematic Overview of the Study



Study drug-dose blind design: Treatment with enoxaparin or JNJ-70033093 will be open-label but blinded to study drug dose and regimen for all subjects randomized to JNJ-70033093. All subjects will receive study drug for 10 to 14 days of randomized treatment, followed by unilateral venography and a follow-up study visit at Week 6.

* No optional dose will exceed a 400-mg total daily dose

** Additional interim analyses will be conducted, as needed, at the discretion of the Operations Committee (OC), and the timing and the cohorts will be defined in the OC charter. These decisions will be made only after taking the safety and efficacy profiles of JNJ-70033093 into account.

1.3. Schedule of Activities (SoA)

Phase	Screening[a]		Postoperative Dosing Phase											Follow-up[b]	
			PO Day 1[c]				PO Day 2	PO Day 4[d]				PO Day 7[d]	PO Day 10-14 (EOD/EW)[f]		
Study Procedures	Up to Day -30	Randomization (up to day of surgery -2)	0h	2h	4h	12h[e]		0h	2h	4h	12h[e]			Week 6 (±10 days)	Unscheduled Visit[g]
Screening/Baseline															
Informed consent[h]	X														
Inclusion/exclusion criteria[i]	X	X													
Medical history and demographics	X														
Bleeding risk history	X														
Relevant prestudy therapy	X														
Urine or serum pregnancy test (WOCBP only)		X											X		
TKR surgery[j]		X													
Study Drug Administration															
Randomization		X													
Dispense/administer study drug[k]		X	X			X	X	X			X	X	X		
Drug accountability													X		
Safety Assessments															
Physical examination[l]	X												X	X	
Efficacy Assessments															
Venography of the operated leg													X[m]		
Symptomatic thrombotic events[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments															
Hematology	X[o]		X[p]				X						X	X	
Serum chemistry	X[o]		X[p]				X						X	X	
Urinalysis	X[o]		X[p]										X	X	
Pharmacokinetics															
PK sample collection[q]				X	X	X	X	X	X	X	X	X	X		X

Phase	Screening[a]		Postoperative Dosing Phase											Follow-up[b]	
			PO Day 1[c]				PO Day 2	PO Day 4[d]				PO Day 7[d]	PO Day 10-14 (EOD/EW)[f]		
Study Procedures	Up to Day -30	Randomization (up to day of surgery -2)	0h	2h	4h	12h[e]		0h	2h	4h	12h[e]			Week 6 (±10 days)	Unscheduled Visit[g]
Pharmacodynamics/ Biomarker															
aPTT, PT, and TGA	X[o]		X[p]	X	X		X	X		X			X		X
FXI clotting activity, anti-FXa activity, and archive sample[r]	X[o]		X[p]		X								X		X
FXI antigen	X[o]														
hs-cTnT	X[o]		X[p]										X		
D-dimer	X[o]		X[p]										X	X	
Ongoing Subject Review															
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events monitoring[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

anti-FXa=anti-Factor Xa; aPTT=activated partial thromboplastin time; EOD=end of dosing; EW=early withdrawal; FXI=Factor XI; h=hour; hs-cTnT=high-sensitive cardiac troponin T; PK=pharmacokinetic; PO=postoperative; PT=prothrombin time; TGA=thrombin generation assay; TKR=total knee replacement; WOCBP=women of childbearing potential

[a] Screening for eligible subjects will be performed within and including 30 days before administration of the first dose of postoperative study drug. Final eligibility must be confirmed prior to randomization and all subjects must be randomized prior to surgery. Subjects can be randomized up to 2 days prior to primary unilateral elective TKR surgery. If the subject has already completed the screening procedures, randomization can occur after a telephone conversation with the subject to verify that there is no significant change in condition, surgery is still planned, and their continued willingness to participate in the study.

[b] Reasonable attempts should be made to conduct the follow-up visit(s) at the scheduled time points. If a subject withdraws from the study before the end of the follow-up phase and is unwilling or unable to return for follow-up visits in person or have follow-up contacts, the study site should collect as much follow-up visit information as possible, including contacting the subject or subject's representative or health care professional by telephone or mail.

[c] All study days will be counted from the first postoperative day of dosing (ie, PO Day 1). The subject's clinical status must be checked again before first dose of postoperative study drug.

[d] Study procedures will be conducted on PO Days 4 and 7 only for those subjects who are still hospitalized.

[e] Assessments may be conducted at 12 hours ±6 hours. In addition, the 12 hour samples on Day 1 and Day 4 should be drawn before the second dose of the day is taken.

[f] Subjects who prematurely discontinue study drug (ie, EW) before the end of the postoperative dosing phase will be instructed to return to the study site at the originally scheduled Day10-14 visit to conduct assessments, including the venography of the operated leg (unless a pulmonary embolism [PE] or symptomatic proximal deep vein thrombosis [DVT] has been diagnosed), and to complete the remaining visits through the Week 6 assessments.

[g] At the discretion of the investigator, subjects may return to the study site between scheduled visits. Subjects should return to the study site for the assessment of any potential bleeding or efficacy endpoint events. Unscheduled PK and pharmacodynamic (PD) samples should be collected as soon as practically possible for any subject who experiences a suspected symptomatic thrombotic or bleeding event.

[h] Must be signed before first study-related activity. At the time of informed consent, 2 alternative means of contact for each subject will be collected (eg, contact information of the subject's children, spouse, significant other, caretaker, legal representative, health care professional).

[i] The investigator will need to determine if the subject is medically appropriate for anticoagulant prophylaxis on the basis of physical examination, medical history, and clinical laboratory tests performed as part of screening for elective TKR surgery. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documents in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

[j] Details regarding the TKR surgery and the post-surgery management (eg, type of anesthesia, procedure duration, cement use, tourniquet use and duration, drain use and volume, use of all mechanical venous thromboembolism [VTE] prophylaxis methods) will be collected in the electronic case report form (eCRF).

[k] Subjects randomized to enoxaparin may initiate treatment at least 12 hours prior to the surgical procedure in accordance with local standard-of-care. If preoperative dosing is implemented following the interim analysis, subjects randomized to JNJ-70033093 will receive a preoperative dose (JNJ-70033093 or placebo) up to 6 hours prior to surgery. All subjects will receive the first postoperative dose (JNJ-70033093 or enoxaparin) while the subject is still hospitalized, with administration beginning a minimum of 12 hours and a maximum of 24 hours after the end of the TKR surgery, defined as the time of wound closure. Subjects will be given a supply of study drug at the time of discharge or transfer to an alternate facility, with instructions to take the study drug, at approximately the same time each day for 10 to 14 postoperative days. Subjects should take the 12-hour dose of study drug on PO Days 4 and 7 only if randomly assigned to JNJ-70033093. The last dose on the Day 10-14 visit will be at the discretion of the investigator and dosing is not required to occur on the day of the venography.

[l] Height and weight should be obtained at the screening visit, with weight only at the final visit. Wounds will be assessed at all visits as part of the adverse event assessment.

[m] Subjects who complete dosing will return to the study site for final EOD assessments (at the Postoperative Day 10-14 visit), at which time unilateral venography of the operated leg will be performed within 1 calendar day after the last dose of either JNJ-70033093 or enoxaparin is taken. If dosing is prematurely discontinued, the venography should be completed on the originally scheduled Day 10-14 (EOD) visit, not earlier. If a subject has suspected symptomatic DVT prior to the Postoperative Day 10-14 visit, an ultrasound will be performed. In these cases, if the ultrasound confirms symptomatic proximal DVT, a subsequent venography assessment is not required. If the ultrasound is negative or confirms a distal DVT, the venography assessment should be conducted on the Day 10-14 visit. In addition, if the subject is objectively diagnosed with a PE meeting the specified definitions prior to Day 10-14, a subsequent venography assessment of the operated leg is not required.

[n] Suspected symptomatic efficacy (thrombotic) events (DVT, PE, death) will be reported by the investigator and reviewed by the Clinical Events Committee (CEC) to ascertain if a thrombotic event has occurred.

[o] Central laboratory specimens must be drawn after signing the informed consent form (ICF) and prior to any potential preoperative doses and prior to surgery. Subjects will be randomized based on the results of standard-of-care local laboratory tests; central laboratory results are not required prior to randomization.

[p] The baseline laboratory assessments, including PD and biomarkers, may be taken at any time on Day 1 (day after surgery) and before the first dose of study drug.

[q] All sites will collect PK blood samples for subjects randomly assigned to JNJ-70033093 at all visits up toPostoperative Day 10-14. The Postoperative Day 1 samples will be drawn at approximately 2, 4, and 12 hours from the oral dosing. The Postoperative Day 2 blood sample will be drawn approximately 24 hours after the first dose of study drug and may be done with the subject as an inpatient or outpatient. Study visits should be conducted in the morning, when possible. Dosing on the day of a study visit will not occur until after the PK sample has been drawn.

[r] Factor XI clotting activity will be assessed in subjects randomly assigned to JNJ-70033093 and anti-FXa activity will be assessed in subjects randomly assigned to enoxaparin. Archive samples will be collected from all subjects at these timepoints.

[s] All adverse events will be reported from the time a signed and dated ICF is obtained until the completion of the subject's last study-related procedure, including all adverse events of special interest (bleeding events, liver enzyme elevations and clinical liver events, and wound or joint complications). All suspected symptomatic efficacy (thrombotic) events will also be captured as adverse events of special interest.

2. INTRODUCTION

JNJ-70033093 (Bristol-Meyers Squibb Company [BMS]-986177) is a small-molecule therapeutic agent that binds and inhibits the activated form of human coagulation Factor XIa (FXIa) with high affinity and selectivity. It is being codeveloped under a collaboration agreement between BMS and its global affiliates and Janssen Pharmaceutical Research and Development, LLC. JNJ-70033093 is being developed as an orally administered anticoagulant for the prevention and treatment of thromboembolic events (eg, venous thromboembolism [VTE]).

JNJ-70033093 is expected to provide noninferior or superior efficacy with reduced bleeding risk versus active comparators. Evidence to support this target profile includes the following:

- Congenital deficiency of Factor XI (FXI) appears to provide protection from both arterial and venous thrombotic events and is rarely associated with unprovoked major bleeding (ie, less bleeding than with other factor deficiencies like Factor X).[18]
- Knockout mice with essentially no FXI develop normally, are resistant to both venous and arterial thrombosis, and do not have any spontaneous bleeding.[37]
- A Phase 2 study in subjects undergoing total knee replacement (TKR) with preoperative dosing of a FXI antisense oligonucleotide (ASO) that resulted in >80% reduction in FXI levels demonstrated superior efficacy compared with enoxaparin 40 mg once daily (total VTE 4% [95% confidence interval {CI}: 1, 12] vs 30.0% [95% CI: 20, 43], p<0.001) with numerically less major or clinically relevant nonmajor bleeding events (3% [95% CI: <1, 9] vs 8% [95% CI: 3, 17], p=0.16).[4]

For the most comprehensive nonclinical and clinical information regarding JNJ-70033093, refer to the latest version of the Investigator's Brochure (IB) for JNJ-70033093.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

2.1. Study Rationale

This study will evaluate the efficacy and safety of JNJ-70033093 in a TKR population. Data from this study will be used, in part, to define the therapeutic window of this FXIa inhibitor. Results from this study will be used to develop Phase 3 studies in subjects requiring anticoagulation, including a possible indication of VTE prevention in subjects undergoing orthopedic procedures.

2.2. Background

Nonclinical Studies

JNJ-70033093 is a high affinity, direct, small-molecule inhibitor of human coagulation FXIa, with an inhibition constant (K_i) of 0.11 nM. JNJ-70033093 has >5,000-fold selectivity for FXIa over other blood coagulation proteases and structurally related enzymes involved in digestion, fibrinolysis, and inflammation, except chymotrypsin and plasma kallikrein where the K_i values are 35 nM and 44 nM, respectively. Human deficiency of plasma prekallikrein is tolerated

without a known phenotype. The protein digestive function of chymotrypsin in the intestine is partially redundant with trypsin. Based on these observations, it is not expected that inhibition of chymotrypsin or plasma kallikrein activity will be a safety concern. To date, nonclinical toxicological studies have not shown any issues attributable to inhibition of either of these enzymes. In standard plasma coagulation assays, JNJ-70033093 produced concentration-dependent increases in activated partial thromboplastin time (aPTT), but not prothrombin time (PT), indicating a selective effect on the intrinsic pathway. In the in-vitro thrombin generation assay (TGA) using human platelet-rich plasma, JNJ-70033093 (0.1 – 10 μM) increased the lag time and time to peak, while reducing peak thrombin and endogenous thrombin potential. In the thromboelastography assay using human whole blood, JNJ-70033093 produced a concentration-dependent increase in the reaction time but did not affect the maximum amplitude. Consistent with its mode of action, JNJ-70033093 did not have any direct effect on platelet aggregation induced by adenosine diphosphate, collagen, or arachidonic acid in human platelet-rich plasma in vitro. Evaluations of the antithrombotic and antihemostatic effects of intravenous (IV) JNJ-70033093 infusions were performed in anesthetized rabbits. JNJ-70033093 caused dose-dependent inhibition of thrombosis formation in injured arteries. In this experiment, the JNJ-70033093 plasma concentrations required to reduce thrombus weight by 20% and 50% were 34.5 ng/mL (55 nM) and 235 ng/mL (375 nM), respectively. In the same model, JNJ-70033093 also restored blood flow to an artery partially occluded by a preexisting thrombus. In this experiment, the JNJ-70033093 plasma concentration required to reduce thrombus weight by 50% was 665 ng/mL (1,060 nM). JNJ-70033093 did not increase bleeding times in rabbits, even at doses that produced approximately 80% inhibition of thrombus formation. The combination of JNJ-70033093, at a dose that produces approximately 80% inhibition of thrombus formation, and aspirin, at a dose that increases bleeding time by approximately 2-fold, did not lead to increased bleeding in rabbits over aspirin treatment alone. Additional rabbit cuticle bleeding-time studies were conducted with JNJ-70033093 in combination with clopidogrel and aspirin. However, off-target effects due to thrombin inhibition (as observed by a 1.8-fold increase in ex-vivo thrombin time coagulation assay) at these high drug exposures observed in rabbits confounded the interpretation of those studies.[21]

Safety Pharmacology

JNJ-70033093, at maximum-tested concentrations of 15.66 to 93.97 μg/mL (serum/protein free), did not exhibit substantial off-target activity against a panel of 42 targets that included G-protein coupled receptors, monoamine neurotransmitter transporters, ligand-gated and non-ligand-gated ion channels, nuclear hormone receptors, or selected enzymes (acetylcholinesterase, monoamine oxidase, and phosphodiesterase). In in-vitro studies, JNJ-70033093 inhibited cardiac human ether-a-go-go gene/rapidly activating delayed rectifier potassium current (hERG/IKr) potassium channel currents, with a concentration at which 50% inhibition was observed (IC_{50}) of 4.2 μg/mL (6.7 μM; 33 times [x] and 14x the projected free/unbound maximum plasma concentration [C_{max}] in humans at 200 mg once daily and twice daily [BID], respectively). At 6.26 μg/mL (10 μM), JNJ-70033093 had minimal effects on cardiac sodium channel currents (22.9% to 25.3% inhibition at 1 and 4 Hz, respectively) and calcium channel currents (13.9% inhibition).[21]

In an exploratory study in anesthetized rabbits, JNJ-70033093 was associated with decreased blood pressure (up to -14.1% pretest) and increased heart rate (up to +20.9% pretest) at plasma concentrations ≥5.7 μg/mL, with prolonged QT interval corrected for heart rate using Fridericia's formula (by ~6.5 ms) also noted at 19.61 μg/mL (13x and 5.5x the projected C_{max} at 200 mg once daily and BID, respectively. In a non-Good Laboratory Practice telemetry study in rats, there were minimal increases in blood pressure (≤5%) at C_{max} ≥5.0 μg/mL and heart rate (≤6%) at C_{max} of 16.14 μg/mL. These rabbit and rat findings were considered nonadverse due to their small magnitude. Importantly, in conscious monkeys, no JNJ-70033093-related hemodynamic or electrocardiogram changes were identified at any dose tested in 2 telemetry studies (C_{max} ≤5.46 μg/mL) or 3 repeat-dose toxicity studies after approximately 2 weeks (C_{max} ≤21.2 μg/mL, electrocardiogram not assessed), 6 weeks (C_{max} ≤7.24 μg/mL), and 9 months (C_{max} ≤6.56 μg/mL) of dosing. The exposure at the no observed adverse effect level (NOAEL) in the 9-month monkey study was 4.3x and 1.8x the projected C_{max} in humans at 200 mg once daily and BID, respectively. Taken together, the in-vitro and in-vivo data indicate low potential of JNJ-70033093 for cardiovascular effects in humans.[21]

Toxicology

The nonclinical safety profile of JNJ-70033093 has been evaluated in a comprehensive battery of in-vitro studies and in-vivo toxicity studies mainly in rats and monkeys. JNJ-70033093 has a high affinity for human FXIa (K_i = 0.11 nM) and cynomolgus monkey FXIa (K_i = 0.15 nM), but has a very weak affinity for rat FXIa (K_i = 490 nM). As such, the rat was chosen for evaluation of potential off-target toxicity, and the monkey was chosen as a non-rodent species to assess both on-target as well as off-target toxicity.

The scope of the toxicology evaluations, as summarized below, supports continued testing of JNJ-70033093 in humans. Unless otherwise specified, exposure multiples at NOAELs and pertinent findings in toxicology studies are expressed relative to the projected exposures at 200 mg once daily (C_{max} of 1.512 μg/mL and area under the concentration versus time curve from 0 to 24 hours of the last measurable concentration [AUC_{0-24h}] of 14.634 μg•h/mL) and 200 mg BID (C_{max} of 3.579 μg/mL and AUC_{0-24h} of 60.514 μg•h/mL), the highest once-daily and BID doses proposed for the Phase 2 study.

The protein binding for of JNJ-70033093 is comparable in rat, monkey, and human sera (97.1%, 89.1%, and 91.5%, respectively). As such, the exposure multiples have not been corrected for free fraction and are expressed as ratios of total exposure unless otherwise specified.

JNJ-70033093 was nongenotoxic in vitro (Ames and cytogenetics assays, tested at maximum concentrations required by the International Council for Harmonisation [ICH] guidelines) and in vivo (micronucleus assessment; conducted as part of a 6-week toxicity study) in rats at doses up to 200 mg/kg/day (AUC_{0-24h} of 319 μg·h/mL; 22x and 5.3x the projected exposure in humans at 200 mg once daily and BID, respectively). Likewise, BMT 210370, an aniline metabolite of JNJ-70033093, was negative in the exploratory assays for mutagenicity and clastogenicity.[21]

In definitive embryo-fetal development studies,[21] JNJ-70033093 was neither embryo-fetal lethal or teratogenic. The exposures at the developmental NOAEL were 11x and 2.7x in rats (166 μg·h/mL) and 4.7x and 1.1x in rabbits (68.4 μg·h/mL) relative to the projected human area under the plasma concentration-time curve (AUC) at 200 mg once daily and BID, respectively.

JNJ-70033093 was well tolerated by rats at all doses tested for 2 and 6 weeks (10, 50, and 200 mg/kg/day) and for 6 months (10, 30, and 50 mg/kg/day).[21] Relative to Day 1 values, AUC exposures to JNJ-70033093 were decreased following repeated dosing. This finding was rat specific, noted in both sexes (with greater effects in males), and most evident in the 6-month study (with Week-26 AUCs 0.3x in males and 0.5x to 0.6x in females, relative to Day-1 values). Other noteworthy findings in rats were limited to increased serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or glutamate dehydrogenase at ≥50 mg/kg/day in the subchronic studies and at ≥10 mg/kg/day in the 6-month study. These findings were considered nonadverse due to their minimal to mild magnitude, transient and/or non-progressive nature with continued dosing, lack of concurrent increases in serum bilirubin suggestive of altered liver function, full reversibility upon dosing cessation, and absence of microscopic evidence of liver injury. The NOAEL in the 6-month study was 50 mg/kg/day and the associated AUC values at Week 26 (26.1 μg•h/mL in males and 96.3 μg•h/mL in females) were ≤6.6x and ≤1.6x the projected exposures in humans at 200 mg once daily and BID, respectively.

JNJ-70033093 was clinically well tolerated by monkeys at all doses tested for 2 weeks (10, 50, and 150 mg/kg/day), 6 weeks (5, 15, and 50 mg/kg/day), and 9 months (10, 30, and 50 mg/kg/day).[21] There was no substantial accumulation or loss of exposures after repeated dosing. Consistent with the intended pharmacology of JNJ-70033093, exposure-dependent prolongations of aPTT were noted at ≥10 mg/kg/day across all studies. At 50 mg/kg/day in the 2-week and 9-month studies, there were also accompanying increases in PT in some monkeys. Overall, the increased aPTT and PT were considered nonadverse as they were not associated with clinical or microscopic signs of bleeding and were fully reversible after cessation of dosing. Additional JNJ-70033093-related changes in monkeys were limited to decreases in red blood cell parameters and serum albumin at ≥50 mg/kg/day in the 2-week study and were considered adverse only in 1 female at 50 mg/kg/day with very high JNJ-70033093 exposure (AUC of 540 μg•h/mL). As such, the high dose in the subsequent 6-week and 9-month studies was capped at 50 mg/kg/day. Based on the absence of adverse findings at any dose tested, the high dose of 50 mg/kg/day was considered the NOAEL for the 9-month study and the associated AUC (76.2 μg•h/mL at Week 39) was 5.2x and 1.3x the projected exposure in humans at 200 mg once daily and BID, respectively.

Collectively, the results of nonclinical toxicology studies demonstrated an acceptable safety profile and support the use of JNJ-70033093 in humans at doses up to 200 mg BID.

Pharmacokinetic Profile

The pharmacokinetic (PK) characteristics of JNJ-70033093 were evaluated in rats, rabbits, dogs, and monkeys after IV and oral dosing.[21] The absolute oral bioavailability of JNJ-70033093 was 18% and 32% in rats and monkeys, respectively. JNJ-70033093 was a substrate of human efflux

transporters including P-glycoprotein (P-gp). After IV administration, the terminal elimination half-life was short (1.4, 2.5, 4.0, and 2.7 hours in rats, rabbits, dogs, and monkeys, respectively) and the total plasma clearance was low in all the species (9% to 23% of the reported liver blood flow). JNJ-70033093 distributed extravascularly in animals. Serum protein binding was 91.5% in human, and 89.1% to 97.1% in animals. Uptake studies with human hepatocytes suggested that active transport processes are at least partially involved in the hepatic uptake of JNJ-70033093. Further studies with rifamycin SV (an organic anion-transporting polypeptide [OATP] inhibitor) suggested that OATPs are not involved in the hepatic uptake of JNJ-70033093 (confirmed in a clinical drug-drug interaction (DDI) study [CV010014]).[21].

In vitro, JNJ-70033093 was the predominant drug-related compound (representing 94% to 99% of total drug-related ultraviolet [UV] peak area) in incubations with liver microsomes or hepatocytes. No unique metabolite was observed in human hepatocyte or microsome incubates. In rats, intact monkeys, and monkeys from a cholecystocentesis study, following a single oral dose of 200-, 150-, and 30-mg/kg, respectively, JNJ-70033093 was the predominant drug-related compound detected in plasma (approximately 99%, 87.2%, and 90.8% of total drug-related UV peak area at C_{max}, respectively). In rats and monkeys, several metabolites were detected including an aniline containing metabolite, Met 17 (BMT 210370), which represented 6% to 36% of the AUC of JNJ-70033093 in monkey, but was present at very low levels in rat plasma (metabolite was nongenotoxic as described later). In monkeys from the cholecystocentesis study, numerous metabolites were detected in bile including BMT 210370. No glutathione conjugate was detected in vitro or in vivo. In bile duct-cannulated rats and monkeys, orally administered [^{14}C] JNJ-70033093 was cleared primarily through biliary elimination.[21] In dogs and monkeys, following IV doses of 0.5 mg/kg, urinary excretion was found to be a minor route of elimination.

Cytochrome P450 (CYP) 3A4/5 was identified as the primary enzyme responsible for the oxidative metabolism of JNJ-70033093. The potential DDIs with CYP3A inhibitors were confirmed in a clinical DDI study. JNJ-70033093 exhibited little or no reversible and time-dependent inhibition of the CYPs. JNJ-70033093 did not inhibit uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzyme (IC_{50} ≥20 μM or 12.5 μg/mL). Relative to the C_{max} values of JNJ-70033093 in humans (6.09 μM or 3.8 μg/mL after 200-mg BID doses), JNJ-70033093 showed low potential to induce the CYP1A2, CYP2B6, or CYP3A4 messenger ribonucleic acid levels in primary human hepatocytes (absence of CYP3A induction confirmed in a clinical DDI study).

JNJ-70033093 was a substrate of P-gp, but not of organic anion transporter (OATPs). JNJ-70033093 inhibited breast cancer resistance protein (IC_{50}=19.6 μM or 12.3 μg/mL), OATP1B1 (IC_{50}=4.8 μM or 3.0 μg/mL), OATP1B3 (IC_{50}=9.7 μM or 6.1 μg/mL), sodium-taurocholate cotransporting polypeptide (NTCP, IC_{50}=19.6 μM or 12.3 μg/mL), bile salt export pump (IC_{50}=7.1 μM or 4.4 μg/mL), multidrug and toxin extrusion (MATE) protein 1 (IC_{50}=9.0 μM or 5.6 μg/mL), and MATE2K (IC_{50}=28.7 μM or 18.0 μg/mL) transporters. No or low inhibition (IC_{50} >50 μM or 31.3 μg/mL) of P-gp, multiple drug-resistance protein (MRP) 2, OAT3, organic cation transporter (OCT) 1, and OCT2 was observed.

Overall, from a perpetrator standpoint and based on the IC_{50} values and observed C_{max} values of 6.09 μM (3.8 μg/mL) in humans (at the highest BID dose of 200 mg proposed for Phase 2), JNJ-70033093 is not anticipated to cause clinically relevant DDIs with substrates of CYPs, UGT1A1, P-gp, NTCP, MRP2, MATE2K, OAT1, OAT3, OCT1, or OCT2 (IC_{50}=19.6 μM to >50 μM). However, there is a potential for DDIs with substrates of OATP1B1, OATP1B3, MATE1, or bile salt export pump at anticipated clinical doses and associated concentrations. In addition, a low potential for gastrointestinal interaction exists with substrates of P-gp and breast cancer resistance protein. From a victim standpoint, there is a potential for DDIs with inhibitors of CYP3A4/5 and P-gp, but not with inhibitors of OATPs.

Clinical Studies

JNJ-70033093 has been and is currently being investigated in a number of studies in humans, including:

- Single- and multiple-ascending dose study
- Drug-drug interaction study with itraconazole, diltiazem, rifampin, and aspirin
- Clinical pharmacology studies of special populations, including subjects with end-stage renal disease (ESRD) undergoing hemodialysis, renal impairment, and hepatic impairment
- Open-label safety and tolerability study in ESRD
- Relative bioavailability
- Japanese PK study
- Secondary stroke prevention study

To date, no dose-limiting safety findings have been observed in these studies.

Human Pharmacokinetics

The first-in-human study with JNJ-70033093 investigated single oral doses between 4 and 500 mg and multiple oral doses between 5 and 500 mg taken over a 14-day period. In the single-dose portion of the study, approximately dose proportional increases were observed between 20 and 200 mg once daily. Coadministration of a high-fat diet resulted in an approximately 1.4-fold increase in exposure at doses of 200 mg while 500 mg of JNJ-70033093 was associated with approximately 2-fold increases in exposure (AUC). Table 1 summarizes the clinical pharmacology of JNJ-70033093.

Table 1: Highlights of Clinical Pharmacology After Administration of Single and Multiple Doses of JNJ-70033093 to Healthy Subjects

PK Properties	JNJ-70033093 Clinical Results
T_{max}	2-4 hrs. Rapid absorption and quick onset PD effect
$T_{1/2}$	~11 hrs (terminal $T_{1/2}$; Supports BID or once-daily dosing
Accumulation index	Accumulation ratio 1.14 – 1.75 (AUC) for dose range 20-500 mg once daily, 3.99 (AUC) for 200 mg BID in MAD
Exposure	Average C_{max}: 15.4 – 7,595 ng/mL; Average AUC: 172-95,110 ng x hr/mL
Proportionality	Greater than dose proportional from 4-20 mg and approximately dose proportional between 20-200 mg in SAD, Greater than dose proportional from 5-20 mg and dose proportional from 20-200 mg, and greater than dose proportional from 200-500 mg in MAD Food effect at 200 mg 1.53- and 1.39-fold (C_{max} and AUC, respectively) Increased food effect at 500 mg (1.8- and 2.1-fold for C_{max} and AUC, respectively)
Metabolites	No significant metabolites
CYP3A4 inhibitors DDI	Itraconazole: 2.5-fold increase in AUC; 1.28 C_{max} Diltiazem: 1.3-fold increase in AUC; 1.09 C_{max} Rifampin: 6.5-fold decrease in AUC; 4.5 C_{max}

AUC=area under the plasma concentration-time curve; BID=twice daily; C_{max}=maximum observed concentration; CYP=cytochrome P450; DDI=drug-drug interaction; hr(s)=hour(s); MAD=multiple-ascending dose; PD=pharmacodynamics; PK=pharmacokinetic; SAD=single-ascending dose; $T_{1/2}$=half-life; T_{max}=time to maximum concentration

Efficacy/Safety Studies

A recently completed multicenter, crossover, randomized, Phase 2a, proof-of-concept study in subjects undergoing hemodialysis for ESRD demonstrated that single doses of JNJ-70033093 up to 300 mg were safe and well tolerated and there were no reports of serious bleeding or other serious adverse events. An exploratory assessment of efficacy showed that the extent of clot formation in the hemodialysis circuit for JNJ-70033093 was similar to the active comparators (unfractionated heparin and enoxaparin), suggesting that JNJ-70033093 has clinically meaningful antithrombotic activity at the doses tested (final clinical study report [CSR] in process).

A recently completed DDI study showed that JNJ-70033093 200 mg BID, taken by healthy subjects over a 12-day period with aspirin, was safe and well tolerated, and the bleeding time did not increase significantly. Subjects enrolled into this study were allowed to take, if clinically indicated, low-dose aspirin (<100 mg once daily).[21]

Detailed information on Phase 1 and 2a studies in JNJ-70033093 is provided in the IB.[21]

2.2.1. Enoxaparin Sodium

The following information, taken from the European Union Summary of Product Characteristics (SmPC), is intended to provide a brief, representative overview of enoxaparin.

Enoxaparin sodium is a low molecular-weight heparin (LMWH), with a mean molecular weight of approximately 4,500 daltons. In the in-vitro purified system, enoxaparin has a high anti-Factor Xa (anti-FXa) activity (approximately 100 IU/mg) and low anti-Factor IIa or antithrombin

activity (approximately 28 IU/mg). These anticoagulant activities are mediated through antithrombin III, resulting in antithrombotic activities in humans. At the recommended doses, enoxaparin sodium does not influence bleeding time and global blood coagulation tests significantly, nor does it affect platelet aggregation or binding of fibrinogen to platelets.

Enoxaparin sodium is indicated in the European Union for the:

- Prophylaxis of thromboembolic disorders of venous origin, in particular those which may be associated with orthopedic or general surgery
- Prophylaxis of VTE in medical patients bedridden due to acute illnesses, including cardiac insufficiency, respiratory failure, or severe infections
- Treatment of venous thromboembolic disease presenting with deep vein thrombosis (DVT), pulmonary embolism (PE), or both
- Treatment of unstable angina and non-Q-wave myocardial infarction (MI), administered concurrently with aspirin
- Treatment of acute ST-segment elevation MI, including patients to be managed medically or with subcutaneous (SC) coronary intervention
- Prevention of thrombus formation in the extracorporeal circulation during hemodialysis

In patients with a higher risk of thromboembolism, such as orthopedic surgery, the recommended dosage of enoxaparin sodium given by SC injection is 40 mg (4,000 IU) once daily, with the initial dose administered at least 12 hours preoperatively.

Enoxaparin treatment is prescribed as standard-of-care for an average period of 10 to 14 days or until the risk of thromboembolism has diminished. A longer treatment duration may be appropriate in some patients following hip replacement, and enoxaparin sodium may be continued for as long as there is a risk of VTE and until the patient is ambulatory. Continued therapy with 40 mg once daily for 3 weeks following initial therapy has been proven to be beneficial in patients post-hip replacement.

For further information regarding enoxaparin refer to the SmPC or United States Prescribing Information. Although the 40-mg once-daily dose of enoxaparin is not approved for TKR in the United States, it has been recently used as a comparator in a number of direct oral anticoagulant (DOAC) studies (eg, ADVANCE-2[28] and RECORD-3[24]).

2.3. Benefit/Risk Assessment

An estimated 920,000 patients in Japan and Europe experience VTE annually, which includes DVT and PE[6,22] and in the United States it is estimated that 900,000 patients experience a VTE annually, with 60,000 being fatal[5]. Joint replacement surgery of the lower extremities carries a high risk of VTE due to prothrombotic processes such as soft tissue and bone injury during surgery, which causes coagulation activation from thromboplastin release, venous stasis from peri- and postoperative immobilization, and inflammation from the healing process.[42] This has led to recommendations in the guidelines that all patients undergoing TKR surgery should receive pharmacologic and/or mechanical VTE prophylaxis.[12,22] Low molecular-weight heparin

and several DOACs, including apixaban, rivaroxaban, dabigatran, and edoxaban have been used in the prevention of VTE in patients undergoing TKR surgery. However, limitations of these drugs include the possibility of an increased risk of bleeding at their recommended dosages. The concern of orthopedic surgeons about bleeding is a major obstacle to the use of anticoagulation in the perioperative period, even when clinical study data show that the absolute risk of bleeding is lower than the risk of VTE.[29]

As an inhibitor to the intrinsic coagulation pathway, JNJ-70033093 directly blocks the amplification process associated with the activation of the intrinsic pathway and the inherent risk of thrombosis associated with activation of this physiologic process. This can occur directly by contact activation of FXI or by thrombin-mediated feedback activation that would occur when the extrinsic pathway is activated. The extrinsic and common coagulation pathways are left intact, allowing for hemostasis to proceed. Therefore, in comparison with current standard-of-care, the use of JNJ-70033093, an inhibitor of a factor component of the intrinsic pathway, may have equal or greater efficacy with a reduced risk of bleeding.

Given that TKR surgery carries a high risk of VTE combined with the hemostatic challenges of surgery, it provides a good setting to evaluate the relative efficacy and safety (bleeding) characteristics of novel anticoagulants.[7] Patients who undergo elective total knee arthroplasty are at a high risk for the development of VTE with a 40% to 60% chance of developing asymptomatic DVT without any form of prophylaxis. It is estimated that 10% to 20% of distal DVT will extend into the proximal veins that carries with it a high risk of embolization and PE. In this setting, upwards of one-third of PEs will be fatal.[19] Therefore, TKR is an appropriate setting for testing new and potentially safer means of anticoagulation.

The available preclinical and clinical evidence suggest that direct inhibition of FXIa by JNJ-70033093 has the potential to reduce the risk of thromboembolic events with a lower risk of major bleeding than currently available DOACs. While bleeding was not observed to any significant degree at the high doses of JNJ-70033093, either in healthy subjects or in those with ESRD undergoing hemodialysis, there is a potential risk of bleeding with any antithrombotic agent. Therefore, subjects will be closely monitored for bleeding, with oversight of the study by the Operations Committee (OC).

More detailed information about the known and expected benefits and risks of JNJ-70033093 may be found in the IB.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To determine the efficacy of JNJ-70033093 in preventing total VTE events (proximal and/or distal DVT [asymptomatic confirmed by venography assessment or objectively confirmed symptomatic], nonfatal PE), or any death during the treatment period.	• Total VTE during the treatment period up to the time of venography as assessed by the CEC. Proof-of-efficacy is reached by either showing a positive dose response or having less than a 30% total VTE event rate in the combined dose group.
Secondary	
• To assess the dose response of JNJ-70033093 for the occurrence of the endpoint of any bleeding events during the treatment period.	• The composite endpoint of any bleeding event on treatment. Any bleeding will be defined as the composite of major, clinically relevant nonmajor bleeding events, or minimal bleeding events assessed by the CEC. Major and clinically relevant nonmajor bleeding events will be assessed according to the ISTH criteria modified for the surgical setting.
• To determine the efficacy of JNJ-70033093 in preventing total VTE events during the full study period.	• Total VTE as assessed by the CEC through Week 6.
• To assess the dose response of JNJ-70033093 for the rate of any bleeding throughout the full study period.	• Occurrence of the composite endpoint of any bleeding events, the composite endpoint of major or clinically relevant nonmajor bleeding events, and the individual components of the composite endpoint of any bleeding as assessed by the CEC through Week 6.
• To assess the dose response of JNJ-70033093 for the prevention of major VTE (death, asymptomatic or symptomatic proximal DVT or PE) during the treatment period and throughout the full study period.	• Major VTE as assessed by the CEC during the treatment period and through Week 6.
• To assess the effect of individual doses of JNJ-70033093 compared with enoxaparin for both efficacy and safety endpoints.	• Total VTE and any bleeding as assessed by the CEC during the treatment period and during the full study period (6 weeks).
• To compare the effect of JNJ-70033093 with enoxaparin for the individual components of the total VTE endpoint.	• All individual components of the primary efficacy endpoint as assessed by the CEC during the treatment period and during the full study period (6 weeks).
• To assess the PK of JNJ-70033093 in men and women undergoing primary unilateral TKR surgery and the relation of these measures to efficacy and safety endpoints (eg, exposure-response analyses).	• Estimation of PK parameters and the effects of demographics and laboratory values (eg, body weight, age, gender, renal function) on the PK of JNJ-70033093. • Estimation of the relationship between JNJ-70033093 exposure levels with probability of total VTE during the treatment period up to the time of venography and the probability of

Objectives	Endpoints
	the composite endpoint of major or clinically relevant nonmajor bleeding events, and the individual components of the composite endpoint of any bleeding event on treatment.
Exploratory	
• To evaluate PD to assess its relationships to PK and the relation of these measures to efficacy and safety endpoints (eg, exposure-response analyses).	• Changes in PD (aPTT, PT, FXI clotting activity, anti-FXa activity, and TGA). • Estimation of the relationship between JNJ-70033093 exposure levels with the changes in PD.
• To evaluate exploratory biomarkers to assess their relationship to the probability of total VTE during the treatment period.	• Estimation of the changes in biomarkers with the probability of total VTE during the treatment period up to the time of venography and the probability of the composite endpoint of major or clinically relevant nonmajor bleeding events, and the individual components of the composite endpoint of any bleeding event on treatment.
• Explore the presence and incidence of asymptomatic MINS as it relates to total knee arthroplasty.	• The presence of an isolated elevated hs-cTnT measurement postoperatively without an alternative explanation (eg, sepsis, atrial fibrillation) in subjects with normal preoperative hs-cTnT. An incremental rise in hs-cTnT without an alternate explanation in individuals with elevated preoperative hs-cTnT.

anti-FXa=anti-Factor Xa; aPTT=activated partial thromboplastin time; CEC=Clinical Endpoint Committee; DVT=deep venous thrombosis; FXI=Factor XI; hs-cTnT=high-sensitive cardiac troponin T; ISTH=International Society on Thrombosis and Haemostasis; MINS=myocardial injury in noncardiac surgery; PD=pharmacodynamic; PE=pulmonary embolism; PK=pharmacokinetic; PT=prothrombin time; TGA=thrombin generation assay; TKR=total knee replacement; VTE=venous thromboembolism

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

The primary hypothesis is that JNJ-70033093 reduces the risk of total VTE during the treatment period. This can be achieved by either a statistically significant dose-response trend or an event rate for the pooled doses of JNJ-70033093 that is statistically lower than 30%. The event rate of 30% is a conservative estimate of the total VTE rate in subjects given placebo.

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, study drug-dose blind, active-controlled, multicenter, dose-ranging study of JNJ-70033093 in subjects undergoing primary unilateral elective TKR surgery. The study uses the prospective, randomized, open-label, blinded endpoint (PROBE) design. Men and women

who are ≥50 years of age are eligible to participate if they are considered medically stable and appropriate for anticoagulant prophylaxis as determined by the investigator and on the basis of clinical laboratory tests performed as part of screening for elective TKR surgery. A target of 1,200 subjects will be randomly assigned to treatment in this study, with an option to increase the randomization target to approximately 1,500 subjects based on interim analysis results and/or evaluability rate.

Subjects meeting all of the enrollment criteria will be eligible to enter the study. The study will be conducted in 3 phases, which includes an up to 30-day screening phase before surgery, a 10- to 14-day postoperative dosing phase, and a 4-week ±10 days follow-up phase. Unscheduled visits may be performed at the discretion of the investigator for the assessment of any potential bleeding or efficacy endpoint events. The total duration of participation following randomization will be approximately 6 weeks.

Screening for eligible subjects will be performed within and including 30 days before administration of the first dose of postoperative study drug. Up to 2 days prior to primary unilateral elective TKR surgery, eligible subjects will be randomly assigned to treatment with either JNJ-70033093 or enoxaparin. If the subject has already completed the screening procedures, randomization can occur after a telephone conversation with the subject to verify that there is no significant change in condition, surgery is still planned, and their continued willingness to participate in the study. Subjects will be unblinded to their treatment assignment but those subjects randomly assigned to JNJ-70033093 will be blinded to the dose and regimen (ie, BID versus once daily). Initially, all subjects randomly assigned to JNJ-70033093 will initiate the study drug the day after TKR surgery (Day 1, 0 hours). Enoxaparin may be initiated postoperatively or preoperatively at least 12 hours prior to the surgical procedure, in accordance with local standard-of-care. Postoperative dosing of both study drugs will occur while the subject is still hospitalized, with administration beginning a minimum of 12 hours and a maximum of 24 hours after the end of TKR surgery, which is defined as the time of wound closure.

Following discharge or transfer to an alternate facility, subjects will continue to take the assigned study drug for a total of 10- to 14-postoperative days as described in Section 6.1, Study Drugs Administered. Unilateral venography assessment of the operated leg will be performed within 1 calendar day after the last dose of either JNJ-70033093 or enoxaparin is taken.

Subjects will return to the study site 6 weeks after the TKR surgery for study-related evaluations and procedures as described in the Schedule of Activities. Safety evaluations will include the monitoring of all adverse events, including nonserious adverse events, serious adverse events, adverse events of special interest (ie, bleeding events, liver enzyme elevations and clinical liver events, wound or joint complications), clinical laboratory tests (ie, hematology, clinical chemistry, urinalysis), and physical examinations. Pharmacokinetic, pharmacodynamic (PD), and biomarker samples will also be collected and assessed.

An OC, Steering Committee, and independent Clinical Events Committee (CEC) will be commissioned for this study. The OC will be unblinded, the Steering Committee will be blinded to the dose and frequency of JNJ-70033093, and the CEC will be blinded to both the study drug

and the dose. The OC will be responsible for reviewing ongoing safety (and efficacy data) by unblinded subject treatment assignments approximately every 4 to 8 weeks. Refer to Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations for details.

An unblinded interim analysis is planned when approximately 400 subjects will have completed the venography or have had a symptomatic VTE event as part of an adaptive approach that will be used to guide the decision to drop and/or add doses of JNJ-70033093, adjust the randomization ratio, and possibly add preoperative dosing of JNJ-70033093. After reviewing the interim analysis data, the OC will have the option to implement or terminate 1 or more JNJ-70033093 dose regimens, including implementing preoperative administration and modifying the once-daily dose regimens. Additional interim analyses will be conducted, as needed, at the discretion of the OC, and the timing and the cohorts will be defined in the OC charter. These decisions will be made only after taking the safety and efficacy profiles of JNJ-70033093 into account.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Intervention Groups

Randomization will be used to minimize bias in the assignment of subjects to study drug and dose groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across study drug groups, and to enhance the validity of statistical comparisons across study drug groups. Subjects will be unblinded as to the study drug assignment (JNJ-70033093 or enoxaparin); however, they will remain blinded to the dose and frequency and the adjudication of clinical endpoint events will be conducted in a blinded fashion by an independent CEC to reduce potential bias during the evaluation of clinical endpoints.

Study Population

Total knee replacement is most commonly performed in older men and women to correct arthritic disease of the joint. Given that the risks of VTE and bleeding increase with age, the study has been appropriately designed to include both men and women who are at least 50 years of age. The risk of VTE following major orthopedic surgery, specifically joint replacement surgery, has been well documented, and the use of postoperative prophylactic anticoagulant therapy is widely accepted as standard-of-care.[12,22] Over the past 20 years, Phase 2 studies of injectable anticoagulants (LMWH, fondaparinux) and newer oral anticoagulants (apixaban, rivaroxaban, dabigatran, and edoxaban) were conducted in this population using venography to detect asymptomatic DVT.[11,17,20,27,28,39]

Choice of Comparator

This study will use LMWH as the comparator for consistency with all of these health-authority approved oral medications that were evaluated in large, similarly designed Phase 3 studies for

the prevention of VTE in TKR surgery and also because it continues to be used widely for prophylaxis. Given that VTE and bleeding-event rates vary across studies, the active control will also provide an internal reference for comparison with JNJ-70033093 in this study.

As one of the most widely used anticoagulants in joint arthroplasty, enoxaparin has been used as a comparator for the currently approved DOACs.[41] Consistent with this approach, enoxaparin was chosen as the comparator in this study. Enoxaparin is approved worldwide for this indication and has demonstrated favorable efficacy and safety (ie, bleeding) results. Refer to Section 2.2.1, Enoxaparin sodium for additional details.

The 40-mg daily dose of enoxaparin will be used in this study as it is the dosage regimen used in approved countries for the indication being studied. Enoxaparin will be administered once daily for 10 to 14 days, with an option to begin the first dose at least 12 hours before surgery, which is preferred by some surgeons, or beginning the next day, 12 to 24 hours after the end of TKR surgery, defined as the time of wound closure.

Choice of Efficacy Measures

Total VTE is a standard efficacy measure for Phase 2 TKR VTE prophylaxis studies. The use of venography to detect asymptomatic DVT and standardized definitions to assess symptomatic venous thromboembolism are specifically recommended as the best approach for the Phase 2 orthopedic surgery setting.[7] The assessment time between Days 10-14 is appropriate given that it is a usual period of anticoagulation following TKR surgery as well as other forms of anticoagulation (eg, DOACs).

Ultrasound is a noninvasive, widely available technique, with a high sensitivity and specificity for symptomatic DVT that has replaced venography in clinical practice for the diagnosis of DVT events (all DVT sensitivity 88%, specificity 96%).[23] However, ultrasound has repeatedly been shown to have very low sensitivity compared with venography for detecting asymptomatic DVT in the postoperative setting.[23,34] In a meta-analysis of 15 studies, the sensitivity of ultrasound compared with venography for detecting asymptomatic DVT was 47%.[23] More recent data are from the Phase 2 studies of rivaroxaban in DVT prophylaxis following hip and knee replacement surgeries, where a substudy (VENUS study) was conducted comparing venography to ultrasound. Despite rigorous methodology, including separate adjudication sites for each technique and a large number of matching pairs of evaluable venography assessments and ultrasounds, the authors concluded that ultrasound cannot replace venography for DVT diagnosis in this setting. The observed frequency of any DVT was 18.9% with venography and 11.5% with ultrasound. The sensitivity of ultrasound compared with venography was 31.1% (95% CI: 23.4, 38.9) for any DVT, 21.0% (95% CI: 2.7, 39.4) for proximal DVT, and 30.8% (95% CI: 23.1, 38.6) for distal DVT. The results for specificity were 93.0% (95% CI: 91.0, 95.1), 98.7% (95% CI: 98.0, 99.5), and 93.3% (95% CI: 91.5, 95.3), respectively.[34]

Therefore, venography is still considered the gold standard and the only reliable method for diagnosing asymptomatic DVT after TKR surgery. The most likely explanations for the poor performance of ultrasound compared with venography in this setting are the nature of the clots

that form early after surgery (small and compressible) compared with symptomatic clots (larger and noncompressible) and the distortion of the veins produced by postoperative swelling.

Although research into new anticoagulants has slowed in recent years, all proof-of-concept studies using the postoperative orthopedic model have continued to use venography to assess the primary endpoint.[4,14,26,40] Venography produces plausible and reliable results in clinical studies[7,19,36] and no anticoagulant has been approved by a health authority for postoperative orthopedic DVT prophylaxis without venography data. Despite the challenges with performing venography, it remains the standard for detecting DVT after TKR surgery and is the most appropriate method for use in this study.

Bilateral venography has been used in most but not all previous Phase 3 studies.[15,17] Venography of the operated leg will be performed in this study. Unilateral venography of the operated leg detects over 90% of DVTs after TKR surgery[16] and exposes subjects to less risk (radiation, contrast dye, venipuncture) and less discomfort.

Choice of Safety Measures/Assessments

Bleeding events are the standard primary safety endpoint in studies of anticoagulant VTE prophylaxis after TKR surgery. Because the occurrence of major bleeding events is infrequent and previous dose-ranging studies have demonstrated that all categories of bleeding events increase with dose in a similar manner, the any bleeding-event composite will be the primary safety endpoint in this study.[25] Published guidelines that describe how to define major bleeding events after major orthopedic surgery will be followed.[35] For nonmajor bleeding events, standardized definitions, as utilized in the Phase 3 TKR studies of apixaban, will be followed.[27,28] All wound or joint complications will also be specifically assessed in this study as these are important from the perspective of both the subject and the surgeon.

Choice of PK Measures

Pharmacokinetic blood samples will be collected and analyzed for subjects who are randomly assigned to treatment with JNJ-70033093 to further understand the PK characteristics and variability and assess the exposure response of JNJ-70033093 in the TKR patient population.

Choice of PD Measures

Samples will be collected to evaluate the PD effect on the target of JNJ-70033093 or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to an intervention. The goal is to evaluate the PD of JNJ-70033093 and aid in evaluating the intervention-clinical response relationship.

Choice of Biomarkers

Myocardial injury after noncardiac surgery is the most frequent vascular complication to occur perioperatively with an estimated frequency of approximately 8%. Affecting about 8 million adults worldwide, patients experiencing myocardial injury in noncardiac surgery (MINS) are at increased risk of death or cardiovascular complication. It is estimated that 85% of MINS occurs within 48 hours of surgery.[8] Unlike the traditional definition of MI, MINS does not require

symptoms or evidence of ischemia (eg, ST changes). In the VISIONS study, only 16% of subjects experiencing MINS had symptoms of an ischemic feature.[2] In an observational study involving a tertiary care center, Rubin and colleagues estimated that the incidence of MINS in orthopedic procedures is approximately 19%.[33]

In this study, subjects will have cardiac troponins drawn preoperatively and postoperatively at approximately 12 to 24 hours and Day 10-14; data derived from these analyses will be used to estimate the early presence of MINS prior to institution of anticoagulation.

Factor XI antigen will also be used as a biomarker for potential bleeding and as an efficacy signal. Recent studies suggest that high levels of FXI are associated with increased risk for venous thrombosis and stroke, whereas reduced FXI levels are associated with protection from VTE. In addition to activation by Factor XIIa, FXI can also be activated by thrombin in a positive feedback reaction, further propagating thrombus growth. Measurement of FXI antigen in plasma at baseline, using a validated immunoassay, may help to improve understanding of thrombotic conditions and help identify subjects susceptible to cardiovascular events.[13,31,44]

4.2.1. Study-Specific Ethical Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

JNJ-70033093 is an investigational drug that is being developed for multiple thrombosis-mediated conditions. The nonclinical and clinical data obtained to date with JNJ-70033093 support administration of multiple doses in a well-controlled clinical research study. The present study is needed to support further clinical development of JNJ-70033093, and the study design is based on sound scientific rationale, as described in this protocol. Thorough scientific evaluation of any promising treatment before marketing authorization is an ethical requirement. In the continuing search for medications with improved efficacy and safety profiles, it is necessary to fully investigate and understand new products.

The primary ethical concern is that the safety and efficacy profile of JNJ-70033093 has not been fully established as it has only been studied in a limited number of subjects. Subjects in this study who are at risk for VTE following TKR surgery are being asked to take a new treatment for the prevention of VTE. Based on the nonclinical and Phase 1 clinical studies, a range of doses of JNJ-70033093 has been selected for further evaluation in this study. Preclinical studies looking at clot formation demonstrated that doses equivalent to 25 mg BID reduced clot formation by 50%.

The primary risk with any anticoagulant drug is the potential for bleeding events. Based on the nonclinical evaluations of JNJ-70033093, the risk for these events is anticipated to be low (ie, all planned doses are below those shown to have a statistically significant increase in bleeding risk). No bleeding signal was detected at the 200-mg BID dose in healthy male subjects. Subjects in this

study will be carefully observed for bleeding events throughout the duration of the study and management strategies for each type of event are outlined in the protocol (see Section 8.2.1.2, Approach to Subjects With a Bleeding Event).

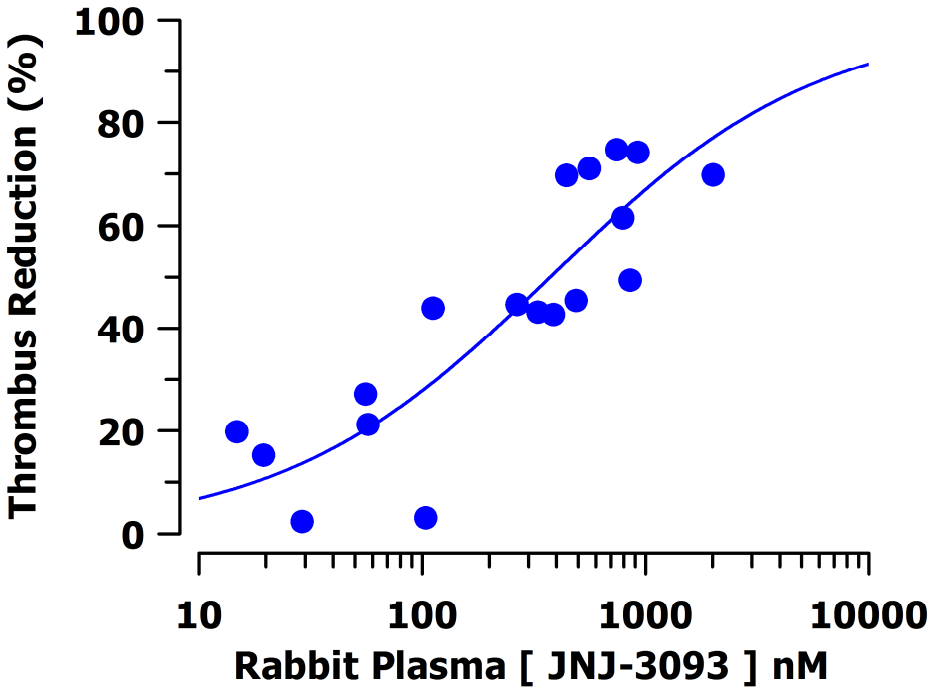
Venography assessments will be used to evaluate for the presence of DVT. The x-ray used in the imaging exposes the body to a small dose of ionizing radiation. The risks of radiation exposure may be tied to the number of x-rays and x-ray treatments a person has had over their lifetime. Given that all subjects in this study will be ≥50 years of age, the incremental risk of this radiation exposure is considered small. X-rays are the oldest and most frequently used form of medical imaging. Other risks associated with venography assessments include pain, infection, and/or bleeding at the site of venous access and the risks from contrast medium administration (ie, allergy, nephrotoxicity, and/or possible irritation of the venous system leading to the development of DVT). In previous studies, venography assessments have been well tolerated and do provide clinically useful information about the presence or absence of DVT following surgery.[32,38]

There may be risks associated with venipuncture and multiple blood sample collection, including prolonged bleeding due to the anticoagulant effects of JNJ-70033093. The total blood volume to be collected for safety, PK, PD, and biomarker laboratory tests is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the World Health Organization (WHO) for standard blood donation volume for healthy donors (standard donation of 350 [body weight >45 kg] to 450 [body weight >50 kg] mL every 12 weeks [males] to 16 weeks [females]).[43]

4.3. Justification for Dose

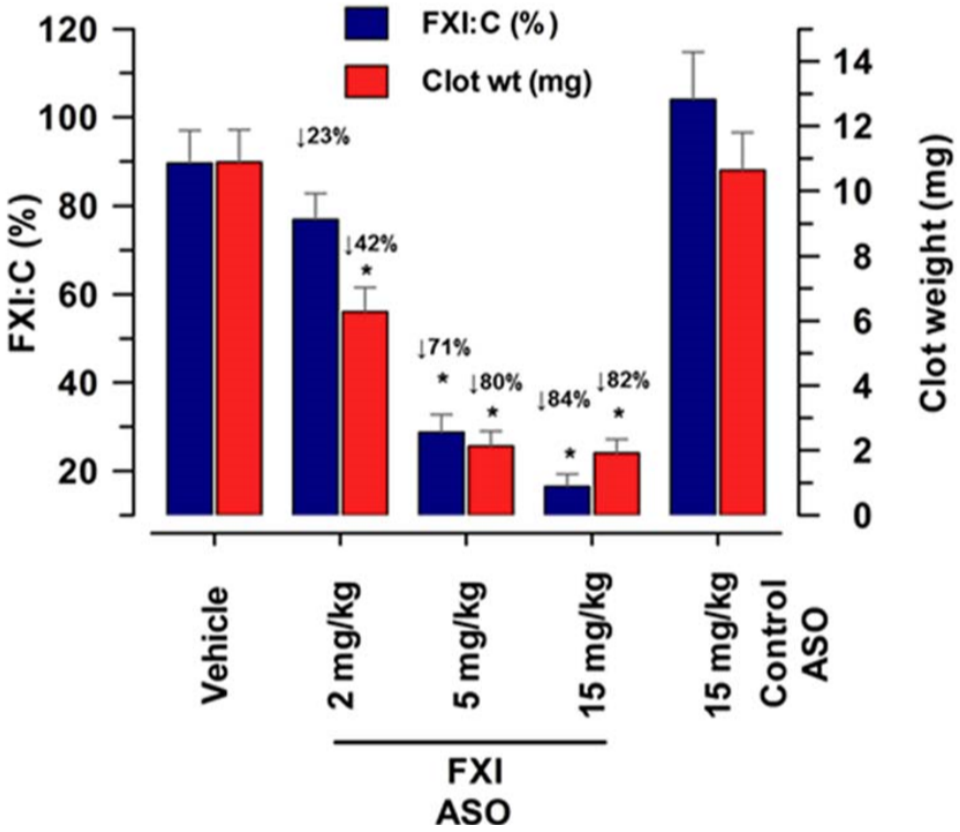
Identification of effective doses of JNJ-70033093 was based on inhibition of thrombus formation in a rabbit model of electrically induced carotid artery thrombus (ECAT) in rabbits. The rabbit ECAT model has been calibrated against clinical results in VTE prevention based on apixaban. In this model, targeting the concentration that led to 50% reduction in thrombus weight was correlated with the steady-state trough concentration of the clinical dose of apixaban. In the rabbit ECAT model, JNJ-70033093 caused a dose-dependent decrease in both clot weight (Figure 2) and preservation of blood flow without a significant increase in bleeding time. The equivalent to half the maximal effective concentration (EC_{50}) plasma concentrations in the rabbit ECAT model was 235 ng/mL (375 nM). Making corrections for the difference in potency in human versus rabbit FXIa (where JNJ-70033093 is more potent than rabbit FXIa) and the differences in plasma protein binding between human versus rabbit (where protein binding is lower in human versus rabbit plasma) yields a human target of 34.5 ng/mL (55 nM) as the trough target concentration.[21]

Figure 2: Exposure-dependent Reductions in Thrombus Weights With JNJ-70033093 in Rabbits



A Phase 2 study for VTE prophylaxis post TKR provides the only published data on the clinical safety and efficacy of reducing FXI activity. Subjects were treated for 36 days prior to surgery with an ASO to reduce the level of FXI. The study showed a dose-dependent reduction in the risk of VTE events compared with enoxaparin. Doses that did not reduce FXI levels to 20% or less of normal did not reduce the risk of VTE events compared with enoxaparin.[4] Figure 3 shows the dose-dependent decrease in FXI levels and clot weight observed in the rabbit ECAT model with ASO-induced inhibition of FXI.[21] Based on the dose-dependent reduction of FXI concentrations observed in the ASO VTE prevention study (ISIS 416158), a trough concentration of approximately 150 ng/mL of JNJ-70033093 was necessary to achieve an antithrombotic effect equal to the 80% reduction in FXI level in the rabbit ECAT model.

Figure 3: Reduction in FXI Concentration Based on FXI ASO Compound Used in Phase 2 VTE Study



ASO=antisense oligonucleotide; C=concentration; FXI=Factor XI; FXI ASO=Factor XI antisense oligonucleotide; VTE=venous thromboembolism

Based on data obtained from healthy subjects, population PK modeling indicates that doses likely to achieve the trough concentration targets based on apixaban and ASO for a VTE prevention study are between 100 to 200 mg once daily and 25 to 50 mg BID. The data indicating coverage of the target concentrations in the rabbit ECAT model for both apixaban and the FXI inhibitor ASO, supports the potential for JNJ-70033093 to provide similar or greater efficacy in patients. Finally, a lower risk of bleeding is anticipated with inhibition of FXIa than with inhibition of Factor Xa (FXa), based on the mechanistic rationale for targeting the intrinsic pathway via inhibition of FXIa.

4.4. End of Study Definition

A subject will be considered to have completed the study if he or she has completed assessments at Week 6 of the follow-up phase or has died prior to Week 6 of the follow-up phase.

Subjects who prematurely discontinue the study drug for any reason before completion of the postoperative dosing phase can be considered to have completed the study if they have completed follow-up at Week 6.

The end of the study is considered the last visit for the last subject in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

5. STUDY POPULATION

Screening for eligible subjects will be performed within and including 30 days before administration of the first dose of postoperative study drug. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling subjects in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 9.1, Sample Size Determination.

5.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Male or female.

2. 50 years of age, or older.

3. Medically stable and appropriate for anticoagulant prophylaxis as determined by the investigator on the basis of physical examination, medical history, and vital signs performed as part of screening for elective TKR surgery.

4. Medically stable and appropriate for anticoagulant prophylaxis on the basis of clinical laboratory tests performed as part of local standard-of-care as part of screening for elective TKR surgery. If the results of laboratory tests are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the investigator.

5. Has plans to undergo an elective primary unilateral TKR surgery.

6. Must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

7. A woman of childbearing potential (WOCBP) must have a negative urine or highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) up to 2 days before the administration of the study drug.

8. A woman must be (as defined in Section 10.5, Appendix 5, Contraceptive and Barrier Guidance and Collection of Pregnancy Information).

    a. Not of childbearing potential

    b. Of childbearing potential and

        - Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method for the duration of study drug with JNJ-70033093 plus 5 half-lives of study drug plus 30 days (duration of ovulatory cycle) for a total of 32 days after the completion of treatment. Examples of highly effective methods of contraception are located in Section 10.5, Appendix 5, Contraceptive and Barrier Guidance and Collection of Pregnancy Information.
        - Pregnancy testing (serum or urine) prior to the first dose of study drug.

9. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 32 days after the last dose.

10. A male subject must wear a condom when engaging in any activity with a WOCBP during the study and for the duration of treatment with JNJ-70033093 plus 5 half-lives of the study drug plus 90 day (duration of sperm turnover) for a total of 92 days after the completion of treatment. Male subjects should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom my break or leak. This criterion does not apply to male subjects randomly assigned to enoxaparin.

11. A male subject must agree not to donate sperm for the purpose of reproduction during the study and for the duration of treatment with JNJ-70033093 plus 5 half-lives of the study drug plus 90 days (duration of sperm turnover) for a total of 92 days after the completion of treatment. This criterion does not apply to male subjects randomly assigned to enoxaparin.

12. Willing and able to adhere to the lifestyle restrictions (Section 5.3, Lifestyle Considerations) specified in this protocol.

5.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. History of any condition for which the use of LMWH is not recommended in the opinion of the investigator (eg, previous allergic reaction, creatinine clearance <30 mL/minute).

2. History of severe hepatic impairment.

3. Planned bilateral revision or unicompartmental procedure.

4. Planned postoperative epidural analgesia with an epidural catheter.

    - If an epidural catheter was used, it must be removed at least 5 hours prior to postoperative study drug administration.

    - If preoperative doses of JNJ-70033093 are implemented following the interim analysis, all subjects may only be randomized if a nerve block and/or general anesthesia is planned.

    NOTE: if a randomized subject had an epidural or spinal anesthesia procedure with bleeding or significant trauma at the time of surgery, they should not receive study drug.

5. Unable to undergo venography (eg, due to contrast agent allergy, poor venous access, or impaired renal function that would increase the risk of contrast-induced neuropathy.

6. Known previous PE or DVT in either lower extremity.

7. Known allergies, hypersensitivity, or intolerance to JNJ-70033093 or its excipients (refer to IB).

8. Contraindications to the use of or known allergies, hypersensitivities, or intolerance to enoxaparin per local prescribing information.

9. Any condition requiring chronic antithrombotic therapy (eg, atrial fibrillation, mechanical heart valve, recent coronary intervention), except for aspirin ≤100 mg per day.

10. Use of strong CYP3A4/P-gp inhibitors or strong CYP3A4/P-gp inducers in the 7 days prior to randomization or the need for ongoing treatment with concomitant oral or IV therapy with strong CYP3A4/P-gp inhibitors or strong CYP3A4/P-gp inducers during the treatment period.

11. Taken any disallowed therapies as noted in Section 6.5, Concomitant Therapy before the planned first dose of study drug.

12. Planned use of intermittent pneumatic compression after the first postoperative dose of the study drug.

13. Received an investigational study drug (including investigational vaccines) or used an invasive investigational medical device within 60 days before the planned first dose of study drug or is currently enrolled in an investigational study.

14. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

15. Has surgery planned (except the TKR study) during the time the subject is expected to participate in the study for which anticoagulant therapy would be interrupted.

16. Previously randomized subject in this study or participated in previous studies with JNJ-70033093.

17. Employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

18. At the time of informed consent, the subject does not agree to following up with scheduled study visits or allowing a telephone contact to the subject's alternative means of contact (eg subject's children, spouse, significant other, caretaker, legal representative, healthcare professional), as necessary, until the end of the study, should he or she discontinue prematurely.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before randomization such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for rescreening. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations. Randomized subjects must also meet these criteria prior to the first dose of the study drug.

5.3. Lifestyle Considerations

Potential subjects must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.5, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. Avoid donating blood for at least 4 days after completion (ie, final follow-up visit) of the study.

4. A WOCBP must agree to use one of the contraceptive methods allowed during the study for a minimum of 32 days after receiving the last dose of study drug as described in Section 10.5 of Appendix 5, Contraceptive and Barrier Guidance and Collection of Pregnancy Information. All men who are randomly assigned to JNJ-70033093 and are sexually active with a WOCBP must agree to use a condom and must also not donate sperm for a minimum 92 days after receiving the last dose of study drug.

5.4. Screen Failures

Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports will identify subjects by subject identification number and age at initial informed consent. In cases where the subject is not randomized into the study, the date seen and age at initial informed consent will be used.

Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Subjects will be eligible for rescreening only in those cases when TKR surgery is rescheduled outside of the 30-day window. Subjects may only be rescreened on 1 occasion.

6. STUDY TREATMENT

6.1. Study Drugs Administered

Drug Administration

JNJ-70033093 will be provided as capsules for oral administration. Subjects will be instructed to take their assigned dose of the study drug orally each day. The study drug is to be taken with approximately 240 mL (8 ounces) of water. The capsules should be swallowed intact and subjects should not attempt to dissolve them in water. Each dose should be taken at approximately the same time each day.

Subjects will be randomly assigned to receive once daily or BID treatment with JNJ-70033093 or enoxaparin 40 mg once daily given subcutaneously for 10 to 14 postoperative days. Prior to the interim analysis, JNJ-70033093 will be initiated postoperatively, while enoxaparin, in accordance with local standard-of-care, may be initiated following the procedure or 12 hours prior to the procedure. At the time of the interim analysis, the OC may implement a preoperative dosing regimen(s) of JNJ-70033093. In this case, preoperative dosing of JNJ-70033093 will occur up to 6 hours before surgery while postoperative administration of the study drug will occur the day after the TKR surgery (Postoperative Day 1, 0 hours), while the subject is still

hospitalized and with a minimum of 12 hours and a maximum of 24 hours after the end of TKR surgery, defined as the time of wound closure.

Study drug administration must be captured in the source documents and the electronic case report form (eCRF). Study-site personnel will instruct subjects on how to store study drugs for at-home use as indicated for this protocol.

Dosing

This study has an adaptive design, with the intent to optimize data collection for the dose-response evaluation using multiple comparison procedures and modeling (MCP-Mod). Prior to the first interim analysis, eligible subjects will be randomly assigned in a 1:1:1:1:1:1:2 ratio to 1 of 7 parallel treatment groups, including 6 dose regimens of JNJ-70033093 or enoxaparin 40 mg once daily given subcutaneously for 10 to 14 postoperative days.

After the interim analysis, the number of dose regimens, the option to implement preoperative dosing, and the randomization ratio will depend on the interim analysis results. However, the number of ongoing doses of JNJ-70033093 is expected to be no less than 4 doses.

Study visits should be conducted in the morning, when possible. Dosing on the day of a study visit should not occur until after the PK sample has been drawn.

JNJ-70033093

Each subject randomly assigned to JNJ-70033093 will take 4 capsules a day, 2 capsules in the morning and 2 capsules in the evening at approximately the same time each day, as follows:

- Group A: JNJ-70033093 25 mg BID (1 capsule JNJ-70033093 25 mg and 1 placebo capsule, BID)
- Group B: JNJ-70033093 50 mg BID (2 capsules JNJ-70033093 25 mg BID)
- Group C: JNJ-70033093 100 mg BID (1 capsule JNJ-70033093 100 mg and 1 placebo capsule, BID)
- Group D: JNJ-70033093 200 mg BID (2 capsules JNJ-70033093 100 mg BID)
- Group E: JNJ-70033093 25 mg once daily (1 capsule JNJ-70033093 25 mg and 1 placebo capsule in the morning and 2 placebo capsules in the evening)
- Group F: JNJ-70033093 200 mg once daily (2 capsules JNJ-70033093 100 mg in the morning and 2 placebo capsules in the evening)
- Optional Group G: JNJ-70033093 (preoperatively or once daily), dose to be determined
- Optional Group H: JNJ-70033093 (preoperatively or once daily), dose to be determined

No optional dose will exceed a 400-mg total daily dose.

If preoperative dose groups of JNJ-70033093 are implemented in the study then all subjects randomly assigned to JNJ-70033093 will receive a preoperative dose of JNJ-70033093 or placebo in order to preserve the blind.

JNJ-70033093 will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

Enoxaparin

Subjects randomly assigned to enoxaparin (Group I) will receive a SC dose of enoxaparin 40 mg once daily, supplied as a prefilled syringe.

6.2. Preparation/Handling/Storage/Accountability

All oral study drug must be stored at controlled temperatures ranging from 36°F to 77°F (2 C to 25°C). Enoxaparin will be stored in accordance with the approved product labeling.

Refer to the pharmacy manual/study-site investigational product and procedures manual for additional guidance on study intervention preparation, handling, and storage.

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner in a disposal container. The disposal container will be retained for verification purposes.

Study drug should be dispensed under the supervision of the investigator or an appropriate delegate and qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Whenever a subject brings his or her study drug to the study site for pill count, this is not considered a return of supplies. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Dynamic central randomization will be implemented in conducting this study. Initially, subjects will be assigned to 1 of 7 study drug groups based on an algorithm implemented in the interactive web response system (IWRS) before the study. Following the interim analysis, the IWRS will be updated for randomization accordingly. Subjects will be stratified by region using dynamic central randomization to minimize the imbalance in the distribution of the number of subjects across study drug groups. Based on the algorithm, the IWRS will assign a unique study drug code, which will dictate the study drug assignment and matching study drug kit for the subject.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the dosing blind for an individual subject.

Subjects will be unblinded as to their treatment assignment but those subjects randomly assigned to JNJ-70033093 will be blinded to the dose and regimen (ie, BID versus once daily). Under normal circumstances, the JNJ-70033093 dosing regimen blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the dose of the treatment by contacting the IWRS. While the responsibility to break the blind in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and time for the unblinding must be documented by the IWRS and reason for the unblinding must be documented in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects randomized to JNJ-70033093 who have had their treatment dose assignment unblinded may continue on study drug unless the subject meets a study drug discontinuation criterion as described in Section 7.1, Discontinuation of Study Drug. Investigators should not disclose the treatment dose assignment to the subject whenever possible, even in a special situation where the treatment dose assignment has been unblinded to the investigator. Subjects who have had their treatment dose assignment unblinded should continue to return for scheduled evaluations.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim analysis is specified, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be

disclosed to those authorized individuals of the OC for the ongoing data reviews and interim analyses, and only for those subjects included in the interim analysis. Refer to Section 10.3, Appendix 3: Regulatory, Ethical, and Study Oversight Considerations for additional details.

Data that may potentially unblind the JNJ-70033093 dose assignment (ie, study drug plasma concentrations, PD and biomarker laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by investigators, the clinical team, or others, as appropriate until the time of database lock and unblinding.

To maintain the blind of the study, the investigator should not measure PD markers (eg, aPTT) locally unless considered necessary for subject clinical care. If performed locally, the results of these laboratory assessments should not be used to determine clinical care. In addition, the investigator will not receive the results of the PD parameters from the central specialty laboratory during the conduct of the study.

6.4. Study Drug Compliance

Drug supplies will be inventoried and accounted for throughout the study. The IWRS will track the study drug dispensed. In addition, the sites will enter the study drug returned by subjects into the IWRS.

Subjects randomly assigned to JNJ-70033093 will be required to return all blister cards at the Day 10-14 visit. For enoxaparin, subjects will be required to return unused study drug at the Day 10-14 visit, at which time study drug accountability will be performed. Start and stop dates and any interruptions will be recorded in the eCRF.

6.5. Concomitant Therapy

Only selected therapies taken before the first dose of study drug (eg, tranexamic acid, antiplatelet therapies, and nonsteroidal anti-inflammatory drugs [NSAIDs]) administered up to 7 days before first dose of study drug must be recorded at screening.

Concomitant therapies, except those medications given as part of the surgical procedure, must be recorded throughout the study beginning with start of the first dose of study drug to the final visit.

All pharmacologic therapies (prescription or over-the-counter medications, including products to manage bleeding, vaccines, vitamins, and herbal supplements) concomitant with and different from the study drug must be recorded in the eCRF. All concomitant non-pharmacologic therapies such as intermittent pneumatic compression devices, foot-pump devices, continuous passive motion devices, compression stockings, electrical stimulation, and acupuncture must also be recorded in the eCRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

The following medications/therapies should not be given concomitantly with the study drug:

- Additional anticoagulant(s) (eg, vitamin K antagonists, Factor IIa or FXa inhibitors). The study drug will be discontinued in subjects who develop any condition that requires long-term anticoagulation (eg, DVT, atrial fibrillation)
- Antiplatelet therapies (eg, platelet adenosine diphosphate P2Y12 receptor antagonist [clopidogrel, ticagrelor, prasugrel]), except for aspirin ≤100 mg/day
- Strong CYP3A4/P-gp inhibitors or strong CYP3A4/P-gp inducers in the 7 days before randomization or concomitant use with the study drug
- Intermittent pneumatic compression after the first postoperative dose of study drug (all mechanical VTE prevention methods such as foot pumps, graduated compression stockings, and continuous passive motion devices are permitted). In those situations where the study drugs are administered preoperatively, intermittent pneumatic compression is still permitted until the time of the first postoperative dose of the study drug.

Nonsteroidal anti-inflammatory drugs should be avoided, if possible, during the study because their use can increase the risk of bleeding and may interfere with collagen formation. If NSAID use is necessary, it is recommended that the minimum dose is used for the shortest possible duration.

6.6. Dose Modification

The assigned dose of JNJ-70033093, matching placebo, and enoxaparin will not be modified during the course of the study. Subjects will receive the full dose of study drug on Day 1 and will remain on their assigned dosages throughout the treatment phase (ie, until Day 10-14 or early discontinuation of the study drug).

6.7. Study Drug After the End of the Study

Subjects will be instructed that study drug will not be made available to them after they have completed/discontinued study drug and that they should return to their primary physician to determine standard-of-care.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

It is imperative for the integrity of the study and results to have complete data. If a subject withdraws from the study before the end of the follow-up phase and is unwilling or unable to return for follow-up visits in person or have follow-up contacts, the study site should collect as much follow-up visit information as possible, including contacting the subject or subject's representative or health care professional by telephone or by email. If applicable, vital status may be obtained by reviewing the subject's medical or public records unless this contact is not permitted per local regulations.

Study drug assigned to a subject that discontinues the study drug or withdraws may not be assigned to another subject. Subjects who withdraw will not be replaced.

7.1. Discontinuation of Study Drug

A subject's study drug must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue the study drug
- Bleeding into a critical site (eg, intracranial, intraspinal, intraocular, pericardial, intra-articular in a nonoperative joint, intramuscular with compartment syndrome, retroperitoneal)
- Drug-induced liver injury meeting the criteria for discontinuation (see Section 8.3.1.3, Liver Enzyme Elevations and Clinical Liver Events)
- Development of any condition that requires open-label treatment with an anticoagulant or other prohibited medication
- The subject requests to discontinue the study drug permanently
- At the (exceptional) request of the sponsor

If a subject discontinues study drug for any reason before the end of the postoperative dosing phase, the assessments should be continued as scheduled.

7.1.1. Temporary Discontinuation

The study drug may be interrupted if a subject develops bleeding or elevated liver enzymes as described in Sections 8.2.1.2, Approach to Subjects With a Bleeding Event and 8.3.1.3, Liver Enzyme Elevations and Clinical Liver Events, respectively.

7.2. Subject Discontinuation/Withdrawal From the Study

A subject will not be automatically withdrawn from the study if he or she has to discontinue study drug before the end of the study drug regimen.

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow up
- Withdrawal of consent

  Withdrawal of consent should be a very unusual occurrence in a clinical study. Subjects who elect to stop the study drug are not automatically considered to have withdrawn consent. The investigator should make every effort to maintain a good relationship with subjects to avoid this occurrence. Withdrawal of consent will be recorded in the eCRF for this study after a discussion between the investigator and the appropriate sponsor representative has taken place.

At the time of signing the ICF, a subject will agree to be contacted to obtain follow-up information should he or she decided to withdraw from the study. If a subject withdraws from the study before the end of the follow-up phase and is unwilling or unable to return for follow-up visits in person or have follow-up contacts, the study site should collect as much follow-up visit information as possible, including contacting the subject or the subject's representative or health care professional by telephone or by email to determine vital status and to collect medical

information related to endpoint events, as agreed to by the subject during the initial informed consent process. For subjects who withdraw consent from study participation, the reasons for the withdrawal of consent should be documented in the source documents and entered in the eCRF. If applicable, vital status may be obtained by reviewing the subject's medical or public records unless this contact is not permitted per local regulations.

For subjects who withdraw consent and are not agreeable to any follow-up contact, it is recommended that the subject withdraw consent in writing, and the subject will be asked to supplement the withdrawal of consent with a signed written statement documenting refusal from all subsequent contact. If the subject refuses or is physically unavailable, the study site should document and sign the reason for the subject's failure to withdraw consent in writing and maintain it with the subject's source records. If the subject chooses to withdraw from the study completely and does not allow further contact by the investigator, then the investigator or designee will consult sources available in the public domain to check the health status of the subject as permitted by local law.

When a subject withdraws consent before completing the study, it is not required for he/she to give a reason. If the reason for withdrawal is known, it should be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Additional subjects will not be entered. If a subject discontinues study drug and withdraws consent from the study before the end, Day 10-14 assessments should be obtained, including the venography of the operated leg (unless a PE or symptomatic proximal DVT has been diagnosed), and the remaining visits through the Week 6 assessments should be completed.

7.2.1. Withdrawal of Consent for the Use of Research Samples

Withdrawal of Consent for the Use of Samples in Future Research

The subject may withdraw consent for use of samples for future research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow Up

If a subject is lost to follow up, every reasonable effort must be made by the study-site personnel to contact the subject and determine their status and the reason for discontinuation/withdrawal, including the possible use of locator agencies to determine vital status, as local laws and regulations permit. The measures taken to follow up must be documented in the subject's source documents. A subject will be considered lost to follow up only after all means of subsequent contact have been exhausted. Refer to Section 7.2, Subject Discontinuation/Withdrawal From the Study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of efficacy, PK, PD, biomarkers, and safety measurements applicable to this study.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: safety (serum chemistry, hematology, urinalysis), PK, PD, and biomarkers. Blood collections for PK, PD, and biomarker assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints, if needed. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

The total blood volume collected for the study is approximately 156 mL (25 mL for safety, 20 mL for PK, and 111 mL for PD/biomarkers.

Additional blood samples may be collected, if necessary, for additional safety, PK, PD, or biomarker assessments based on emerging data, but the maximum amount of blood drawn from each subject in this study will not exceed 200 mL without prior Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and health-authority approvals. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples and do not require prior IEC/IRB and health-authority approvals.

Volume of Blood to be Collected From Each Subject

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Approximate Total Volume of Blood (mL)[a]
Safety (including screening and post-intervention assessments)			
- Hematology	2.0	5	10
- Serum chemistry	2.5	5	12.5
Serum β-hCG pregnancy tests[b]	2.5	1	2.5
PK samples	2.0	10	20
PD and biomarker samples			
- aPTT and PT	4.5	8	36
- TGA	4.5	8	36
- FXI clotting activity or anti-FXa activity	1.8	4	7.2
- hs-cTnT	2.7	3	8.1
- FXI antigen	1.8	1	1.8
- Archive sample	2.7	4	10.8
- D-dimer	2.7	4	10.8
Approximate Total[c]			155.7

anti-FXa=anti-Factor Xa; aPTT=activated partial thromboplastin time; β-hCG=beta-human chorionic gonadotropin; FXI=Factor XI; hs-cTnT= high-sensitive cardiac troponin T; No.=number; PD=pharmacodynamics(s); PK=pharmacokinetic(s); PT=prothrombin time; TGA=thrombin generation assay

a. Calculated as the number of samples multiplied by amount of blood per sample.
b. If a serum β-hCG pregnancy test is required, it will be performed by the study site's local laboratory.
c. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples and are not included in the total volumes.

Note: An indwelling IV cannula may be used for blood sample collection.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. It is important to record the exact date and time for PK sample collection even if the time deviates from the scheduled time of collection. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (or equivalent) and charged with a volume equal to the dead space volume of the lock.

Refer to the Schedule of Activities for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manuals that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB
- Pharmacy manual/study-site investigational product and procedures manual
- Laboratory manuals for clinical, PK, PD, and biomarker laboratory specimens
- IWRS Manual
- Electronic data capture (eDC) Manual
- Sample ICF
- Venography manual
- Guidelines for reporting bleeding-event verbatim terms
- Subject contact cards (wallet card)
- Contact information page

8.1. Efficacy Assessments

Efficacy evaluations will include unilateral venography assessment of the operated leg and assessments of symptomatic DVT, PE, or death to assess the primary, secondary, and exploratory efficacy outcomes.

8.1.1. Assessments for DVT

Venography assessments of the operated leg will be performed by injecting contrast agent into a foot vein and obtaining x-ray images of the proximal and distal leg veins. Evaluable venography assessments require the visualization of all the deep veins except for the muscular, anterior tibial, and deep femoral veins. An ultrasound will be performed in those subjects with suspected

symptomatic DVT prior to the Postoperative Day 10-14 visit. In these cases, if the ultrasound confirms symptomatic proximal DVT, a subsequent venography assessment is not required. If the ultrasound is negative or confirms a distal DVT, the venography assessment should be conducted on the Day 10-14 visit.

Study-specific venography assessment training will be provided to each study site. Each study site will be responsible for identifying at least 1 primary person to perform the venography assessments for subjects. Evaluability of the venography assessments based on centrally adjudicated data will be monitored for each site on an ongoing basis. If venography assessment performance is considered not acceptable, then further randomization by the investigator may be suspended until additional training or retraining is provided. Additional details regarding the venography procedure and study-specific training requirements will be provided in a venography manual, which will be provided separately to the study sites.

8.1.2. Assessments for PE

For all subjects with symptoms of PE, spiral computed tomography, pulmonary angiography, or perfusion/ventilation lung scanning combined with chest radiography will be performed. A diagnosis of PE will be made only if the subject has symptoms of PE (eg, sudden onset of dyspnea, chest pain, or fainting), and 1 of the following criteria is met:

- Positive spiral computed tomography scan of the chest revealing a segmental or more proximal thrombus
- Positive pulmonary arteriogram
- High probability ventilation/perfusion lung scan (defined as 1 or more segmental or large [>75% of a segment] subsegmental perfusion defects associated with ventilation mismatch)
- Intermediate probability ventilation/perfusion lung scan and ultrasound or venographic evidence of DVT
- Autopsy confirmation

If a subject is objectively diagnosed with a PE meeting the specified definitions prior to Day 10-14, a subsequent venography assessment of the operated leg is not required.

8.2. Safety Assessments

The safety and tolerability of JNJ-70033093 will be evaluated throughout the study according to the timepoints provided in the Schedule of Activities by the assessment of adverse events, including nonserious adverse events, serious adverse events, adverse events of special interest (ie, bleeding events, liver enzyme elevations and clinical liver events, and wound or joint complications), clinical laboratory tests (ie, hematology, clinical chemistry, urinalysis), and physical examinations. All bleeding events will be classified according to the definitions of bleeding events in Section 10.6, Appendix 6, Definition of Bleeding Events. Safety evaluations may also be performed at unscheduled timepoints, if deemed by the investigator or appropriate designee as necessary to ensure the safety of the subject. All suspected symptomatic efficacy (thrombotic) events will also be captured as adverse events of special interest.

The OC will be responsible for reviewing ongoing safety (and efficacy data) by unblinded subject treatment assignments approximately every 4 to 8 weeks. They will also review the interim analysis data and make dose decisions, including but not limited to deciding whether to proceed with the optional cohorts and at what dose(s). Details regarding the OC are provided in Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the adverse event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities.

8.2.1. Bleeding Events

8.2.1.1. Classification of Bleeding Events

All subjects will be observed for signs and symptoms of bleeding events throughout the study and at each study visit as indicated in the Schedule of Activities.

The investigator's classification of bleeding events according to the protocol classification will be collected in the eCRF (Section 10.6, Appendix 6, Definition of Bleeding Events). Additional information, including but not limited to the list below, will be collected for subjects with bleeding events and captured in the source documents and entered into the eCRF:

- Location of the bleeding and duration
- Provocation of the bleeding
- Association with any procedure
- Action taken regarding the study drug
- Concomitant or additional treatment given for this bleeding event
- Any associated hemoglobin (and/or hematocrit) levels
- Hospitalization (or prolonged hospitalization) due to bleeding events
- Outcome

All available information related to the classification of bleeding events will be collected and adjudicated by the independent CEC.

8.2.1.2. Approach to Subjects With a Bleeding Event

If a subject has a bleeding event requiring intervention during the study, the following measures should be considered:

- Discontinue the study drug (refer to Section 7.1, Discontinuation of Study Drug)
- Usual treatment measures for bleeding events, including local pressure, fluid replacement and hemodynamic support, blood transfusion, and fresh frozen plasma, if physical examination and laboratory testing suggest that benefit could be obtained
- Other causes besides antithrombotic medication can be contributory to the seriousness of the bleeding event (ie, rule out disseminated intravascular coagulation, thrombocytopenia, and other coagulopathies, kidney and liver dysfunction, concomitant medications) and should be treated accordingly
- Depending on local availability, consultation with a coagulation expert should be considered

Currently, there is no reversal agent for JNJ-70033093; however, the anticoagulant effect of JNJ-70033093 dissipates in 48 to 72 hours. At therapeutic doses, the anticoagulant effects of JNJ-70030393 will not be reflected by international normalized ratio (INR) values but may be reflected by prolongation of aPTT. In-vitro spiking of human plasma with JNJ-70033093 resulted in concentration-dependent increases in aPTT, which is consistent with its mechanism of action. Pre-incubation with activated 4-factor prothrombin concentrate complex (FEIBA) and Factor VIIa (Novo-Seven®), 2 commercially available nonspecific reversal agents, were able to prevent JNJ-70033093-induced prolongations in aPTT. These data demonstrate that FEIBA (and Factor VIIa by bypassing FXIa inhibition), can promote clotting and provide hemostasis.[9] Furthermore, FEIBA was able to reverse bleeding induced by a FXIa-inhibitor compound in a rat-tail transection model of bleeding in anesthetized rats.[10]

Therefore, if bleeding cannot be controlled by these measures, administration of FEIBA or Factor VIIa according to the dosages and dosing schedules that are recommended in their respective package inserts could be considered (Note: consultation with a coagulation expert is recommended before use).

Protamine sulfate partially reverses the anticoagulant activity of enoxaparin. For subjects receiving enoxaparin, if bleeding cannot be controlled by the above measures protamine can be considered at the dosages recommended in the SmPC.

8.2.2. Physical Examination

The physical examination consists of a routine medical examination that includes general appearance and a review of the following systems: neurologic, eyes/ears/nose/throat, thyroid, cardiovascular, respiratory, abdominal/gastrointestinal, hepatic, musculoskeletal, and dermatologic. Any bleeding observed during the examination (eg, skin, gingiva, nares) will be recorded as a potential bleeding event as described in Section 8.2.1.1, Classification of Bleeding Events. Additional body systems or further detailed physical examinations (eg, rectal examinations) should be performed if considered clinically appropriate by the investigator. Physical examinations will be performed by the investigator or a designated health

care professional who is licensed and/or certified in accordance with applicable local laws to perform physical examinations.

Height and weight should be obtained at the screening visit, with weight only on the final visit.

The physical examination will be conducted at the time points indicated in the Schedule of Activities. An assessment of the wound will be made at all visits as part of the adverse event assessment. Any new, clinically significant findings (in the opinion of the investigator) that were not noted at the time of the screening visit must be captured as adverse events and will be followed to resolution.

8.2.3. Vital Signs

Vital signs measurements are not being collected in this study.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be collected as noted in Section 10.2, Appendix 2, Clinical Laboratory Tests. The investigator or appropriate designee must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

At screening, the investigator will need to determine that the subject is medically appropriate for anticoagulant prophylaxis on the basis of clinical laboratory tests performed as part of local standard-of-care as part of screening for elective TKR surgery. Hematology and chemistry laboratory tests and a urine sample for urinalysis will be obtained at screening and before dosing (0 hour) and will be performed by the central laboratory. Refer to Section 10.2, Appendix 2, Clinical Laboratory Tests for the list of tests to be performed by the central laboratory.

8.3. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study.

Because this study involves subjects who are scheduled to undergo a medically indicated surgical procedure, anticipated events will not be recorded and reported. However, considering that this is one of the first studies to evaluate JNJ-70033093 in subjects, all adverse events and serious adverse events are important in understanding the safety of the study drug and will be collected for the duration of the study.

For further details on adverse events and serious adverse events (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up, and Reporting.

8.3.1. Adverse Events of Special Interest

In this study, adverse events of special interest are:

- Bleeding events
- Wound or joint complications
- Liver enzyme elevation and clinical liver events

  Note: As previously noted in Section 8.2, Safety Assessments, all suspected symptomatic efficacy (thrombotic) events will also be captured as adverse events of special interest. Asymptomatic DVT found on the planned Day 10-14 venography assessment does not need to be reported as an adverse event unless it meets the criteria for a serious adverse event (eg, prolonged hospitalization). Information from these asymptomatic events will be reported on the venography assessment eCRF.

8.3.1.1. Bleeding Events - Adverse Events of Special Interest

Refer to Section 8.2.1, Bleeding Events, for further details on the classification of bleeding events as well as the approach to use with subjects who present with a bleeding event.

8.3.1.2. Wound or Joint Complications

All subjects will be observed for signs and symptoms of wound or joint complications throughout the study and at each study visit as indicated in the Schedule of Activities. The wound will be evaluated by the investigator for any abnormal bleeding, swelling, redness, drainage, or infection. Any joint complications such as bleeding/hematoma, infection or prosthesis malfunction (eg, limited range of motion) will also be recorded as adverse events of special interest. Any medical or surgical treatments for wound or joint complications will be recorded as well.

8.3.1.3. Liver Enzyme Elevations and Clinical Liver Events

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur before the reporting of a potential drug-induced liver injury. Subjects meeting the following criteria for liver-related laboratory abnormalities must be reported as adverse events of special interest and have blinded study drug discontinued immediately:

- ALT and/or AST ≥5x the upper limit of normal (ULN) for ≥7 consecutive days, confirmed by repeat
- ALT and/or AST ≥10x ULN, confirmed by repeat*

Treatment with the blinded study drug should be interrupted if:

- ALT and/or AST ≥3x ULN, confirmed by repeat*

*NOTE: If the ALT and/or AST elevation occurs within 1 calendar day of surgery and the repeat to confirm the elevation is ≥25% lower than the initial elevation, with the repeat testing performed at least 24 hours after the first sample, the study drug does not have to be immediately discontinued or interrupted. The value should be checked every 48 to 72 hours and if it continues to decrease the study drug can be continued.

Subjects with abnormal liver function tests should be followed until the ALT/AST returns to <2x ULN or to baseline prior to considering the restart of treatment with the blinded study drug, but no later than the scheduled Day 10-14 visit.

A potential drug-induced liver injury is defined as:

- ALT or AST elevation ≥3x ULN

  AND

- Total bilirubin ≥2x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

  AND

- No other immediately apparent possible causes of transaminase elevation and hyperbilirubinemia, including but not limited to: viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drug(s) known to be hepatoxic

8.3.2. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All adverse events and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

8.3.3. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events

Solicited adverse events are predefined local and systemic events for which the subject is specifically questioned. In this study, subjects will be queried directly to solicit potential bleeding events using general questions about any bleeding and specific questions about common minor bleeding events that could be overlooked by the subject (eg, bruising, gingival bleeding, epistaxis).

Unsolicited Adverse Events

Unsolicited adverse events are all adverse events for which the subject is not specifically questioned.

8.3.4. Follow Up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up, and Reporting.

8.3.5. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs as per regulatory requirements to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified. The determination of the expectedness in the SUSARs will use the IB for JNJ-70033093 and the SmPC for enoxaparin.

8.3.6. Pregnancy

All initial reports of pregnancy in all female subjects or partners of male subjects randomly assigned to JNJ-70030393 must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. If a subject becomes pregnant during the study, a determination regarding study drug discontinuation must be made by the investigator in consultation with the sponsor.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.4. Treatment of Overdose

For this study, the accidental or intentional administration of any dose of JNJ-70033093 that is considered both excessive and medically important will be considered an overdose. The sponsor does not recommend specific intervention for an overdose. There is no known antidote for overdose with JNJ-70033093 and no studies have been performed to assess methods of reversing JNJ-70033093 absorption effects; however, in theory, activated charcoal may reduce the absorption of JNJ-70033093 if given early after administration of JNJ-70033093.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor listed in the Protocol Contact Page immediately.
- Closely monitor the subject for adverse event/serious adverse event and laboratory abnormalities until JNJ-70033093 can no longer be detected systemically (at least 2 days).
- Monitoring aPTT may be of help in determining the extent of anticoagulation.
- Obtain plasma samples for PK and PD (aPTT and PT) analysis as soon as possible from the date of the last dose of study drug if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose (number of capsules), the nature (accidental, intentional) as well as the duration of the overdosing in the eCRF.
- Report overdose as a serious adverse event.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

8.5. Pharmacokinetics

Plasma samples will be used to evaluate the PK of JNJ-70033093. Plasma collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

8.5.1. Evaluations

Venous blood samples of approximately 2 mL will be collected and divided into 2 aliquots for measurement of plasma concentrations of JNJ-70033093. All samples should be timed from the first postoperative dose taken. The dosing date and time of each dose of JNJ-70033093 on the preceding day will also be recorded in the eCRF. Subjects who experience a suspected bleeding event or symptomatic thrombotic event should have PK samples collected as soon as practically possible after the event occurs.

Samples collected for analyses of JNJ-70033093 plasma concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study

period for the evaluation of relevant biomarkers. Additional information about the collection, handling, and shipment of biological samples can be found in the PK Laboratory Manual.

8.5.2. Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of JNJ-70033093 using a validated, specific, and sensitive (eg, liquid chromatography-mass spectrometry/mass spectrometry) method by or under the supervision of the sponsor. Pharmacokinetic samples will be collected from all subjects randomly assigned to JNJ-70033093. Detailed instruction for the PK blood collection, labeling, processing, storage, and shipping will be provided to the study site in the procedures manual.

In addition, residual plasma PK samples may be stored for future analysis of the metabolite profile, if needed. If these analyses are conducted, they will be reported separately from the CSR.

The Schedule of Activities lists the sampling schedule to be followed for the assessment of PK. In addition to the times listed in the table, a sample for measurement of JNJ-70033093 plasma concentration should be collected as close to practically possible for any subject who experiences a suspected symptomatic thrombotic or bleeding event, or if requested by the Medical Monitor (determined on a case-by-case basis) in the event of an overdose.

8.5.3. Pharmacokinetic Parameters and Evaluations

Parameters

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters (eg, apparent clearance, apparent volume of distribution) and exposure levels for exposure-response analysis of JNJ-70033093 and associated variables will be derived using population PK modeling. Baseline covariates (eg, body weight, age, sex, creatinine clearance, race) may be included in the model, if relevant. The analysis of these parameters will be outlined in the population PK modeling plan and reported separately from the CSR.

Pharmacokinetic/Pharmacodynamic Evaluations

The relationship between the observed plasma concentration of JNJ-70033093 and measured PD markers will be investigated graphically. If appropriate, PK/PD exposure and response-relationships may be further analyzed quantitatively.

The relationships between the plasma PK exposure levels of JNJ-70033093 derived from the population PK model will be correlated with the measured PD markers and safety/efficacy endpoints via graphical analysis. When necessary, these data may be analyzed statistically using a suitable model. The details of the analyses plan will be presented in a population PK modeling plan that is separated from the Statistical Analysis Plan (SAP). The results will be reported separately from the CSR.

8.6. Pharmacodynamics

Venous blood samples will be collected for PD evaluation of aPTT, PT, FXI clotting activity, anti-FXa activity, and TGA at the timepoints specified in the Schedule of Activities. Factor XI clotting activity will be assessed in subjects randomly assigned to JNJ-70033093 and anti-FXa activity will be assessed in subjects randomly assigned to enoxaparin. Subjects who experience a suspected bleeding event or symptomatic thrombotic event should have PD samples collected as soon as practically possible after the event occurs. Additional information about the collection, handling and shipment of biological samples can be found in the PD laboratory manual.

Activated Partial Thromboplastin Time

Activated partial thromboplastin time is a measure of the intrinsic and final common pathways of the coagulation cascade. It represents the time, in seconds, for plasma to clot after addition of phospholipid, an intrinsic pathway activator, and calcium. The name 'Activated Partial Thromboplastin Time' comes from the original form of the test in which only the phospholipid concentration of the test was controlled (as opposed to the phospholipid and the surface activator concentrations) and the name 'partial thromboplastin' was applied at the time to phospholipid preparations that accelerated clotting but did not correct the prolonged clotting times of hemophilic plasma. The term 'partial' means phospholipid is present but no tissue factor. The normal and reference ranges vary depending on reagent and instrument combinations, particularly with the phospholipid composition. It is used to evaluate the coagulation Factors XII, XI, IX, VIII, X, V, II (prothrombin), and I (fibrinogen) as well as prekallikrein and high molecular-weight kininogen. Heparin, DOACs, and direct thrombin inhibitors, including hirudin, argatroban, and dabigatran have an effect on the assay. Blood will be collected for measurement of changes in aPTT clotting time.

Prothrombin Time

Prothrombin time is a global clotting test that is used for the assessment of the extrinsic pathway of the blood coagulation cascade. It is a 1-stage test based upon on the time required for a fibrin clot to form after the addition of tissue factor (historically known as tissue thromboplastin), phospholipid, and calcium to decalcified, platelet-poor plasma. The test is sensitive for deficiencies of fibrinogen and Factors II, V, VII, and X, with sensitivity being best for Factors V, VII, and X and less pronounced for Factor II. Prothrombin time and the normalized version, INRs are used to monitor warfarin therapy. It should be noted that currently, 3 types of PT reagents are used: recombinant thromboplastins, tissue thromboplastins (which are usually from rabbit brain or human placenta), or combined thromboplastins (tissue thromboplastin diluted into fibrinogen). These reagents differ in factor sensitivity, heparin responsiveness, lot-to-lot consistency, and absolute value of the clotting times.

Factor XI Clotting Activity

Factor XI clotting activity is determined utilizing an aPTT-based 1-stage clotting time assay. Serial dilutions of normal pooled plasma are mixed with FXI-depleted plasma and the clotting times are measured according to standard aPTT protocol, to establish a reference range. Subject

test plasma is treated in the same way and compared with the reference plasma. The assay will be performed at a specialty laboratory.

Anti-Factor Xa Activity

The plasma anti-FXa assay is used to monitor factor unfractionated heparin and LMWH. The plasma anti-FXa assay provides an accurate assessment of LMWH activity. Factor Xa is added to plasma containing a FXa-specific substrate and substrate hydrolysis is measured. A standard curve is generated by measuring the FXa chromogenic activity in control plasma samples that contain known concentrations of LMWHs. Chromogenic activity in patient plasma is then compared to the standard curve to determine the LMWH level.

Thrombin Generation Assay

The TGA is a global coagulation assay that evaluates the thrombogenic capacity of a plasma sample and has been proposed that it may better reflect prothrombotic or hemorrhagic states than conventional clotting assays. In the traditional TGA, coagulation of citrated plasma is initiated through the extrinsic pathway by adding tissue factor, phospholipids, and calcium. For this study, a kaolin slurry will be used instead to initiate coagulation through the contact activation pathway. Using this approach, a Factor X-specific TGA can also be performed by diluting test plasma into FXI-deficient plasma and measuring kaolin-induced thrombin generation, similar to the approach used for FXI-specific clotting. Thrombin generation is continuously monitored through the product released by cleavage of a thrombin-specific fluorogenic substrate. The generated thrombogram is used to determine several relevant parameters, including endogenous thrombin potential, defined as the net amount of thrombin that test plasmas can generate based on the relative strength of the pro- and anticoagulant reactions.

Archive Sample for Exploratory Research

Blood samples will be collected at the time points specified in the Schedule of Activities and a plasma sample archived for future exploratory PD research related to the safety and/or efficacy of JNJ-70033093. Refer to the PD laboratory manual for detailed instructions for sample collection, processing and shipment of archive samples for exploratory research.

8.7. Biomarkers

Venous blood samples will be collected for measurement of D-dimer, high-sensitive cardiac troponin T (hs-cTnT), and FXI antigen assessment at the timepoints specified in the Schedule of Activities.

D-dimer

The various states of coagulation activation that occur in vivo lead to the production of thrombin and then, cross-linked fibrin. What follows is a reactive fibrinolysis, during which plasmin breaks down fibrin. D-dimer is the ultimate degradation product of cross-linked fibrin. The presence of D-dimer in plasma is an indirect marker of a coagulation activation followed by a reactive thrombolysis. Increased levels D-dimer can be found in patients with DVT, PE, disseminated intravascular coagulation, hemorrhages, surgery, cancers, and severe infections.

The D-dimer assay is an enzyme immunoassay procedure for the quantitative determination of D-dimer levels.

High-sensitive Cardiac Troponin T

The troponin complex, consisting of troponin C, T, and I subunits, regulates the contraction of striated muscles. Damage to cardiac muscle tissue causes release of troponins into the bloodstream and circulating troponin levels correlate to the degree of muscle damage; accordingly, cardiac troponins are considered primary biomarkers for diagnosis of acute MI and risk assessment in acute coronary syndrome. Immunoassays are performed to detect cardiac troponin T in plasma samples prepared from venous blood collection.

Factor XI Antigen

Measurement of FXI antigen in plasma at baseline, using a validated immunoassay, may help to improve understanding of thrombotic conditions and help identify subjects susceptible to cardiovascular events.

8.8. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

This study will use an adaptive design intended to optimize data collection for dose-response modeling. It is estimated that approximately 1,200 subjects will be randomly assigned to treatment in this study, with an option to increase to approximately 1,500 subjects based on interim analysis results and/or evaluability rate. Subjects will be randomly assigned to postoperative BID doses of JNJ-70033093 25, 50, 100, 200 mg, postoperative once-daily doses of JNJ-70033093 25 and 200 mg, and enoxaparin 40 mg once daily in a 1:1:1:1:1:1:2 randomization ratio until the interim analysis, which will occur when approximately 400 subjects will have completed the venography or have had a symptomatic VTE event. The dose regimens and randomization ratio may be adjusted post-interim analyses, depending on the interim analysis results and safety review. These adjustments include dropping ineffective dose regimens or dose regimens with safety concerns (especially bleeding) as well as adding dose regimens (ie, once daily dose and/or preoperative dose regimens). The randomization ratio will be modified to optimize data collection for dose-response estimation.

9.1. Sample Size Determination

Assuming the evaluability rate (rate of subjects with a valid assessment of potential efficacy outcome and who take at least 1 dose of study drug) is 80%, if the true underlying total VTE event rates are as shown in Table 2, the study is expected to have over 99% power to declare

proof-of-efficacy at a 1-sided, 5% α-level. Proof-of-efficacy is defined as either a statistically significant dose-response trend or primary endpoint event rate for the pooled BID JNJ-70033093 groups that is statistically lower than 30%. The exact power will vary because of the nature of the adaptive study design.

Comparison with enoxaparin will be based on the comparison between the highest postoperative dose with acceptable safety and enoxaparin. For example, if the highest dose for acceptable safety is 200 mg BID, the number of evaluable subjects at this dose and enoxaparin groups is expected to be 120 and 240 subjects respectively, the power to detect a statistically significantly lower total VTE event rate against enoxaparin, at 1-sided, 5% α-level, is over 90%.

Table 2: Assumed Total VTE Event Rates by Treatment Group in Sample Size Determination

	JNJ-70033093				Enoxaparin 40 mg once daily
	25 mg	50 mg	100 mg	200 mg	
BID	18%	14.5%	12.5%	11.0%	
Once daily	24%			14%	23.8%

BID=twice daily VTE=venous thromboembolism

9.2. Populations for Analyses

For purposes of analysis, the following populations are defined in Table 3:

Table 3: Analysis Populations

Population	Description
ITT	(as termed Full Analysis Set in the ICH E9 guideline): This population consists of all randomized subjects who have a signed valid informed consent.
mITT	This population is a subset of the ITT population, consisting of subjects who take at least 1 dose of the study drug and have a valid assessment of potential efficacy outcome at the Day 10-14 visit and the Week 6 visit.
Safety	This population is a subset of the ITT population, consisting of subjects who receive at least 1 dose of the study drug.

ICH=International Conference on Harmonisation; ITT=intent to treat; mITT=modified intent to treat

The valid assessment of potential efficacy outcome is defined as subjects meeting 1 of the following.

- Had an evaluable venography at the Day 10-14 visit
- Had symptomatic DVT or PE at the Day 10-14 visit and the Week 6 visit
- Died before the Day 10-14 visit and before the Week 6 visit

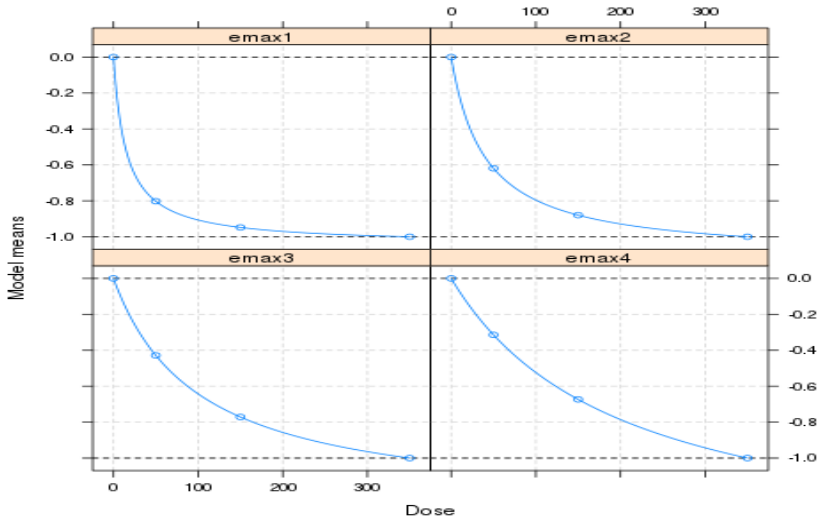
9.3. Statistical Analyses

9.3.1. Efficacy Analyses

The study objectives include proof-of-efficacy and estimation of dose-response relationship in total VTE. These 2 objectives will be addressed by a unified (modified) MCP-Mod

approach,[1,3,30] utilizing collective data from postoperative regimens. Proof-of-efficacy will be established by either a statistically significant dose-response trend, or by a statistically lower total VTE event rate in pooled BID postoperative data compared with 30%. The rate of 30% is a conservative estimate of the total VTE rate in subjects given placebo. The trend test consists of contrast tests defined by prespecified candidate models (4 E_{max} dose-response modules with varying degrees of ED_{50}, Figure 4), which provide estimates of dose response (taking BID and once daily into consideration). Note that data from preoperative dose regimens will not be used in the modified MCP-Mod analysis. They will be analyzed separately.

Figure 4: Canonical Candidate E_{max} Dose-response Models Used in the MCP-Mod Analysis



The efficacy of the drug is established when the maximum of the t-test statistics for the dose-response trend exceeds the critical value. Predicted event rates at a specific dose will be derived for the candidate model.

The details of the adaptive decision guidelines will be specified in the OC charter and the SAP.

Because study drug may be started before TKR surgery in selected treatment groups, randomization will be done prior to the surgery. Some subjects are expected to be no longer eligible to participate in the study due to their medical conditions after the surgery, such as excessive bleeding or other complications. As a result, there will be a non-negligible proportion of subjects who do not receive any study drug. To reduce biases induced by these subjects, subjects who do not receive any study drug will be excluded from the primary analysis. However, they will be included in sensitivity analyses as defined in the SAP.

The primary analyses of efficacy endpoints will be based on CEC-adjudicated events from the mITT population. The primary efficacy endpoint and its components will be summarized by dose and treatment group. Prespecified clinical variables of interest for the efficacy subgroup analyses include region, age, sex, body mass index, renal function, surgery duration, and tourniquet use.

9.3.2. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Study drug-emergent adverse events are adverse events with onset during the postoperative dosing phase or that are a consequence of a preexisting condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summaries, listings, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue the study drug due to an adverse event, or who experience a severe or a serious adverse event.

Adverse events of special interest are bleeding events, wound or joint complications, and liver enzyme elevations and clinical liver events. Subjects with adverse events of special interest may be counted or listed.

The safety population will be a subset of the ITT population consisting of subjects who take at least 1 dose of the study drug. The analyses of bleeding adverse events will be based on the CEC-adjudicated events; all other nonefficacy or nonbleeding adverse events will be based on investigator-reported events in the safety population.

Estimation of the dose-response relationship in any bleeding will be addressed by a unified (modified) MCP-Mod approach as with efficacy. Any bleeding, major bleeding, clinically relevant nonmajor bleeding, composite of major or clinically relevant nonmajor bleeding, and minimal bleeding will be summarized by the dose and treatment group. The same variables specified for the efficacy subgroup analyses will be used for the safety subgroup analysis with the addition of aspirin/nonsteroidal anti-inflammatory drugs.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Physical Examination

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

9.3.3. Other Analyses

Pharmacokinetic Analyses

Population PK analysis of plasma concentration-time data of JNJ-70033093 will be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline subject characteristics (ie, demographics, laboratory variables, genotypes, race) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Data will be listed for all subjects with available plasma concentrations per treatment group. Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study intervention; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All subjects and samples excluded from the analysis will be clearly documented in the study report.

For each treatment group, descriptive statistics, including arithmetic mean, standard deviation (SD), coefficient of variation, median, minimum, and maximum will be calculated for all individual derived PK parameters including exposure information of JNJ-70033093.

All plasma concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations or SAS dataset. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the CSR.

Descriptive statistics will be used to summarize JNJ-70033093 plasma concentrations at each sampling time point.

Exposure-response analyses will be conducted to explore the relationship of the plasma concentration of JNJ-70033093 with efficacy and safety endpoints. The details of the analyses plan will be presented in a population PK modeling plan that is separate from the SAP. The results will be reported separately from the CSR.

Pharmacodynamic and Biomarker Analyses

Descriptive statistics, including mean, median, SD, minimum, and maximum will be provided for the percent change from baseline of the PD (aPTT, PT, FXI clotting activity, anti-FXa activity, TGA) and biomarker (D-dimer, hs-cTnT, FXI antigen) parameters by nominal time of collection and dose and regimen level. The parameters may be statistically analyzed using mixed models.

Pharmacokinetic/Pharmacodynamic Analyses

The relationship between observed plasma concentration of JNJ-70033093 and measured PD markers will be investigated graphically. If appropriate, PK/PD exposure and response relationships may be further analyzed quantitatively.

The relationship between the plasma PK exposure levels of JNJ-70033093 derived from the population PK model will be correlated with the measured PD markers and safety/efficacy endpoints via graphical analysis. When necessary, these data may be analyzed statistically using a suitable model. The details of the analyses plan will be presented in a population PK modeling plan that is separate from the SAP. The results will be reported separately from CSR.

9.4. Interim Analysis

A planned, unblinded interim analysis will be conducted by the OC as part of the adaptive approach that will occur when approximately 400 subjects will have completed the venography or have had a symptomatic VTE event. The interim analysis results will be used to guide the decision to drop and/or add doses of JNJ-70033093, adjust the randomization ratio, and possibly add preoperative dosing of JNJ-70033093 based on available efficacy and safety data. If PK/PD analysis results are available at the time of the interim analysis, the results will be included in the review. After reviewing the interim analysis data, the OC will have the option to implement or terminate 1 or more JNJ-70033093 dose regimens, including implementing preoperative administration and modifying the once-daily dose regimens. Additional interim analyses will be conducted, as needed, at the discretion of the OC and the timing and the cohorts will be defined in the OC charter. A futility analysis will also be included as part of the interim analysis, which may lead to stopping the entire study. These decisions will be made only after taking the safety and efficacy profiles of JNJ-70033093 into account. Further details related to the first interim analysis and any subsequent interim analyses as determined to be appropriate by the OC as well as the decision guidelines will be specified in the OC charter.

9.4.1. Committees

An OC, Steering Committee, and independent CEC will be established as noted in Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ALT	alanine aminotransferase
anti-FXa	anti-Factor Xa
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24h}	area under the concentration versus time curve from 0 to 24 hours of the last measurable concentration
β-hcg	beta-human chorionic gonadotropin
BID	twice daily
BMS	Bristol Meyers Squibb Company
CEC	Clinical Events Committee
CI	confidence interval
C_{max}	maximum plasma concentration
CSR	clinical study report
CYP	cytochrome P450
DDI	drug-drug interaction
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
ECAT	electrically induced carotid artery thrombus
eCRF	electronic case report form
eDC	electronic data capture
ESRD	end-stage renal disease
FSH	follicle stimulating hormone
FXa	Factor Xa
FXI	Factor XI
FXIa	Factor XIa
GCP	Good Clinical Practice
hs-cTnT	high-sensitive cardiac troponin T
IB	Investigator's Brochure
IC_{50}	concentration at which 50% inhibition was observed
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
IWRS	interactive web response system
K_i	inhibition constant
LMWH	low molecular-weight heparin
MATE	multidrug and toxin extrusion
MCP-Mod	multiple comparison procedures and modeling
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MINS	myocardial injury in noncardiac surgery
mITT	modified intent to treat
MRP	multiple drug-resistance protein
NSAID	nonsteroidal anti-inflammatory drug
NTCP	sodium-taurocholate cotransporting polypeptide
NOAEL	no observed adverse effect level
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
OC	Operations Committee
OCT	organic cation transporter

PD	pharmacodynamic(s)
PE	pulmonary embolism
P-gp	p-glycoprotein
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PROBE	prospective, randomized, open-label, blinded endpoint
PT	prothrombin time
RBC	red blood cell
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
TGA	thrombin generation assay
TKR	total knee replacement
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
UV	ultraviolet
VTE	venous thromboembolism
WBC	white blood cell
WHO	World Heath Organization
WOCBP	woman of childbearing potential
x	times

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory:

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count
Red blood cell count
Hemoglobin
Hematocrit</td><td><u>Red Blood Cell (RBC) Indices:</u>
MCV
MCH
% Reticulocytes</td><td><u>White Blood Cell (WBC) (Complete Blood Count) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen (BUN)
Creatinine
Glucose, nonfasting
AST/Serum glutamic-oxaloacetic
ALT/Serum glutamic-oxaloacetic
Gamma-glutamyltransferase (GGT)</td><td>Total bilirubin
Direct bilirubin (if total bilirubin >2x ULN)
Alkaline phosphatase
Lactic acid dehydrogenase (LDH)
Uric acid
Calcium
Phosphate
Albumin
Total protein
Cholesterol
Triglycerides
Magnesium</td></tr>
<tr><td colspan="3">Note: Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.3.1.3, Liver Enzyme Elevations and Clinical Liver Events.</td></tr>
<tr><td rowspan="2">Routine Urinalysis</td><td colspan="2"><u>Dipstick</u>
Specific gravity
pH
Glucose
Protein
Blood
Ketones
Bilirubin
Urobilinogen
Nitrite
Leukocyte esterase</td><td><u>Sediment (if dipstick result is abnormal)</u>
RBCs
WBCs
Epithelial cells
Crystals
Casts
Bacteria</td></tr>
<tr><td colspan="3">If dipstick result is abnormal, flow cytometry will be used to measure sediment. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.</td></tr>
</table>

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the principal investigator, where required.
- Signed and dated Clinical Trial Agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable

- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1, Study-Specific Ethical Design Considerations.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

INFORMED CONSENT PROCESS

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for their surgery or postoperative care. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without

violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, which includes permission to obtain information about his or her survival status.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject is obtained.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory PD, biomarker, and PK research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand JNJ-70033093, to understand thrombosis, to understand differential intervention responders, and to develop tests/assays related to JNJ-70033093 and VTE prophylaxis. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal of Consent for the Use of Research Samples).

COMMITTEES STRUCTURE

Operations Committee

An OC will be established for this study. The OC, consisting of clinicians with expertise in thrombosis, thromboprophylaxis, hematology, orthopedic surgery, and clinical studies, and also including clinical and biostatistics representatives from the sponsor (not directly involved in study monitoring), will review ongoing unblinded safety and efficacy data. The OC will be responsible for:

- Reviewing ongoing safety (and efficacy data) by unblinded subject treatment assignments approximately every 4 to 8 weeks
- Reviewing the interim analysis data and making dose decisions, including but not limited to deciding whether to proceed with optional cohorts and at what dose(s)

The details of the OC function and composition, as well as dose decision guidelines will be described in the OC charter.

Steering Committee

A Steering Committee with expertise in thrombosis, thromboprophylaxis, hematology, orthopedic surgery, and clinical studies will be commissioned to provide scientific leadership the study. The Steering Committee will be responsible for providing advice to the sponsor in an effort to ensure the scientific validity and integrity of the study and for the publication of results. The Steering Committee will receive recommendations from the OC regarding suggested modifications to the study based on the review of the unblinded data by the OC. The sponsor, in collaboration with the Steering Committee, will ultimately decide whether to accept the recommendations and will oversee the implementation of any modifications, if applicable. Details regarding the composition, roles, and responsibilities of the Steering Committee will be documented in a separate charter.

Independent Clinical Events Committee

An independent CEC will be established to review, adjudicate, and classify endpoint events as they become available in a blinded, consistent, and unbiased manner according to the definitions

provided in the CEC charter. Committee members will not have direct operational responsibilities for the conduct of the study, nor will they directly enroll subjects or be involved in study monitoring. Further details regarding the composition, roles, and responsibilities of the CEC will be documented in a separate charter.

The CEC will have responsibility for reviewing, adjudicating, and classifying the following assessments and study endpoint events or events that appear suggestive of a study endpoint event:

- Venography assessment
- Suspected symptomatic DVT
- Suspected symptomatic PE
- Suspected bleeding events
- Death

The CEC will verify all components of the bleeding and efficacy endpoint events. The CEC will centrally adjudicate all clinical events based on the endpoint definitions. The CEC will remain blinded to treatment assignment. All necessary source documents will be sent to the CEC in a blinded fashion to enable adjudication and verification of events. The CEC-adjudicated and investigator-reported results on efficacy and safety outcomes will be provided for the interim analysis. The CEC-adjudicated events will be used in the final analysis.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding JNJ-70033093 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-70033093, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a CSR generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of PK, PD, and biomarker analyses performed after the CSR has been issued will be reported in a separate report and will not require a revision of the CSR.

Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study-site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

MONITORING

The sponsor will use a combination of monitoring techniques: central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study-site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

ON-SITE AUDITS

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

STUDY AND SITE CLOSURE

Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.2, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death.
- Is life threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is a suspected transmission of any infectious agent via a medicinal product.
- Is Medically Important.*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must

be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-70033093, the expectedness of an adverse event will be determined by whether or not it is listed in the IB. For enoxaparin, the expectedness of an adverse event will be determined by whether or not it is listed in the SmPC.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed below (see Attribution Definitions).

ATTRIBUTION DEFINITIONS

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant treatment(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant treatment(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant treatment(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant treatment(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

SEVERITY CRITERIA

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study drug in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

PROCEDURES

All Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number

- Subject number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a subject in a study through Week 6, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

CONTACTING SPONSOR REGARDING SAFETY

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators,

and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 8.3.2, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Subjects must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.6, Pregnancy, and Section 10.4, Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT (**PREFERRED** METHOD FOR COMPOUNDS WITH POSSIBLE OR UNKNOWN TOXICITY AND **RECOMMENDED** METHOD FOR COMPOUNDS WITH SUSPECTED OR DEMONSTRATED TOXICITY) **Highly Effective Methods That Are User Independent** *Failure rate of ≤1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of >1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be

consistent with local regulations regarding the use of contraceptive methods for subject in clinical studies.

b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study drug.

c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.6. Appendix 6: Definition of Bleeding Events

1. Major Bleeding in Surgical Setting[35]
   a. Fatal bleeding, and/or
   b. 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
   c. Extrasurgical site bleeding causing a fall in hemoglobin level of 20 g L)-1 (1.24 mmol L-1) or more, or leading to transfusion of 2 or more units of whole blood or red cells, with temporal association within 24 to 48 hours to the bleeding, and/or
   d. Surgical site bleeding that requires a second intervention open, arthroscopic, endovascular, or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection, and/or
   e. Surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be an associate fall in hemoglobin level of at least 20 g L-1) (1.24 mmol L-1), or transfusion, indicated by the bleeding, of at least 2 units of whole blood or red cells, with temporal association within 24 hours to the bleeding.
2. Clinically Relevant Nonmajor Bleeding[27,28]

Clinically relevant nonmajor bleeding is defined as any bleeding event that is:

- Acute clinically overt bleeding
  - Does not satisfy additional criteria required for the bleeding event to be defined as a major bleeding event and meets at least 1 of the following criteria:
    - Epistaxis (nose bleed):
      - Subject seeks medical attention from a physician
      - Subject visits an emergency room
      - Bleeding requires an intervention (eg, nasal pack)
      - Single bleeding episode persists for 5 minutes or more
    - Gastrointestinal bleed:
      - Vomit containing frank blood or coffee-ground material, which tests positive for blood
      - Endoscopically confirmed bleeding
      - Frank blood per rectum or melenic stools
    - Hematuria:
      - Overt, spontaneous bleeding
      - Bleeding (bloody urine) persists for 24 hours or more after instrumentation

- Bruising/ecchymosis:
  - Any bruise that is assessed as "unusual" (eg, greater than expected following surgery)
- Hemoptysis:
  - Expectoration of blood or blood-stained sputum
- Hematoma:
  - Overt blood collection with the surgical wound
  - Presence of a hematoma is demonstrated radiographically (eg, ultrasound, computed tomography, magnetic resonance imaging) and a drop of hemoglobin is present with no external evidence of bleeding

Note: Any bleeding event not meeting major or clinically relevant nonmajor criteria will be recorded as minimal bleeding.

10.7. Appendix 7: Protocol Amendment History

This is an original protocol.

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INVESTIGATOR AGREEMENT

JNJ-70033093

Clinical Protocol 70033093THR2001

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): John Strony, MD

Institution: Janssen Research & Development

Signature: _____ Date: 12 Dec 2018

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Approved, Date: 11 December 2018

Janssen Research & Development *

Clinical Protocol

Protocol Title

A Randomized, Open-Label, Study Drug-Dose Blind, Multicenter Study to Evaluate the Efficacy and Safety of JNJ-70033093 (BMS-986177), an Oral Factor XIa Inhibitor, Versus Subcutaneous Enoxaparin in Subjects Undergoing Elective Total Knee Replacement Surgery

Short Title

A Randomized Study to Evaluate the Safety and Efficacy of Oral JNJ-70033093 Versus Enoxaparin in Subjects Undergoing Elective Total Knee Replacement

AXIOMATIC-TKR - Antithrombotic treatment with factor **XI**a inhibition to **O**ptimize **M**anagement of **A**cute **T**hromboembol**ic** events in **TKR**

Protocol 70033093THR2001; Phase 2

JNJ-70033093

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

JNJ-70033093 (BMS-986177) is being codeveloped under a collaboration agreement between Bristol-Myers Squibb Company (BMS) and Janssen Pharmaceuticals, Inc. (Janssen).

US sites of this study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

EudraCT NUMBER: 2018-004237-32

Status:	Approved
Date:	10 September 2019
Prepared by:	Janssen Research & Development, LLC
EDMS number:	EDMS-ERI-172187276, 2.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	10-Sep-2019
Amendment JPN-1	24-July-2019
Original Protocol	11-Dec-2018

Amendment 1 (10 September 2019)

Overall Rationale for the Amendment: The overall reasons for the amendment are to modify the study design with regards to the planned and optional doses and to remove the option for preoperative dosing.

Section Number and Name	Description of Change	Brief Rationale
Title Page	The study name "**AXIOMATIC-TKR** - **A**ntithrombotic treatment with factor **XI**a inhibition to **O**ptimize **M**anagement of **A**cute **T**hromboembol**ic** events in **TKR**" was added to the title page.	The title page was revised to include the study name for better readability.
1.1. Synopsis Objectives and Endpoints; 3. Objectives and Endpoints	Parenthesis placement was moved in the primary objective to include all deaths in the definition of total venous thromboembolism (VTE).	Editorial error in the primary objective did not align with efficacy evaluations in the assessment of study outcomes.
1.1. Synopsis Objectives and Endpoints; 1.1. Synopsis Hypothesis; 3. Objectives and Endpoints	The hypothesis and the primary endpoint were revised to specify that the event rate will be analyzed by the "combined twice daily (BID) dose group" instead of the "combined dose group". Also, the secondary endpoint was modified in regard to the bleeding criteria because there is no International Society on Thrombosis and Hemostasis (ISTH) assessment for clinically relevant nonmajor bleeding in the surgical setting.	The language pertaining to the hypothesis, primary and secondary endpoints modified for enhanced clarity.
1.1. Synopsis Overall Design; 4.1. Overall Design; 8.2. Safety Assessments; 9. Statistical Considerations; 10.3. Appendix 3, Regulatory, Ethical, and Study Oversight Considerations, Committees Structure/Operations Committee	Text specifying the frequency of reviews of unblinded data by the Operations Committee (OC) was changed from approximately every 4 to 8 weeks to 3 to 8 weeks.	The frequency of reviews of unblinded data was modified as agreed upon with the OC.
1.1. Synopsis, Overall Design; 1.2. Schema; 4.1. Overall Design; 9. Statistical Considerations; 9.4. Periodic and Interim	The number of subjects to be included at the first interim analysis was changed from 400 to approximately 300 subjects (approximately 50 subjects in each of the JNJ-70033093 BID treatment groups). In addition, the text noting that the timing and	The number of dose groups at the onset of the study was reduced by 2 groups, therefore, the timing of the first interim analysis was changed. Because this is the first small-

Section Number and Name	Description of Change	Brief Rationale
Analyses	the cohorts will be defined in the OC charter was removed.	molecule that inhibits the activated form of human coagulation Factor XIa, flexibility was needed in determining the timing of the interim analyses during OC review of the data.
1.1. Synopsis; 1.2. Schema; 4.1. Overall Design; 6.1. Study Drugs Administered	The option to administer preoperative doses of JNJ-70033093 was removed throughout the protocol.	Academic leadership advised that preoperative dosing would not be adopted by the orthopedic community in clinical practice, therefore testing was removed from the protocol.
1.1. Synopsis; 1.2. Schema; 6.1. Study Drugs Administered; 6.3. Measures to Minimize Bias: Randomization and Blinding; 9. Statistical Considerations	• Once daily dose regimens of JNJ-70033093 were moved from the start of the study to possible doses after the interim analysis and the doses were changed from 25 mg once daily and 200 mg once daily to 50 mg once daily and 200 mg once daily. • Initial randomization changed from 1:1:1:1: 1:1:2 to 1:1:1:1:2 • Initial number of dose groups changed from 7 to 5 • Removed text noting the number of ongoing doses of JNJ-70033093 is expected to be no fewer than 4 doses.	The once daily doses were re-evaluated, and the 50 mg once daily dose will be evaluated because it more closely parallels the 25 mg BID dose and will allow for a more meaningful comparison between the once daily and BID doses.
1.1. Synopsis, Number of Subjects; 1.2. Schema; 4.1. Overall Design; 9. Statistical Considerations	Target and maximum number of subjects was changed from 1,200 and 1,500 to 900 and 1,200, respectively. Text revised to specify that this is based on the possible addition of once daily doses and/or the evaluability rate. It was also clarified that the number of subjects who were planned to be randomized into the dropped dosing regimen can be allocated to one of the other dosing groups.	The target number of subjects was changed based on the change in the study design.
1.1. Synopsis; 1.3. Schedule of Activities (SoA); 4.1. Overall Design; 4.2. Scientific Rationale for Study Design; 6.1. Study Drug Administered	• Regarding the first dose of study drug, the specification for "the day after total knee replacement (TKR) surgery" was changed to "after the end of TKR surgery" and "next day" was removed. • "PO" was removed in front of days of the visit • 10- to 14- postoperative days was changed to 10 to 14 days. • Postoperative Day 10-14 visit was changed to Day 10-14. • Footnote "r" added to SoA to specify optional pharmacodynamic (PD) samples for subjects randomized to enoxaparin.	During initiation of the study it was determined that standard-of-care in certain regions should initiate anticoagulation on the day of surgery, not the morning after surgery. Collection of the PD sample was made optional for enoxaparin subjects in order to make dosing on the evening of surgery more practical.
1.1. Synopsis; 1.2. Schema; 6.1. Study Drug Administered/Drug	Enrollment in Group E was discontinued. Subjects randomized to this group prior to Amendment 1 will continue treatment.	Once daily study drug-dose groups revised to reflect changes in the study design and allow

Section Number and Name	Description of Change	Brief Rationale
Administration	Enrollment in Group F was suspended and made optional until the OC determines that enrollment is appropriate. For Group G, the 50 mg once daily dose was added (2 capsules JNJ-70033093: 25 mg in the morning and 2 placebo capsules in the evening). Text noting that enrollment in Group G will become optional per Amendment 1 was also added. Optional Group H removed. Text noting that no optional dose will exceed a 400-mg total daily dose was removed.	flexibility of optional dosing in Groups F and G until final determination by the OC.
1.1. Synopsis, Study Drug Groups and Duration; 1.3. Schedule of Activities (SoA), Footnote 1; 4.1. Overall Design; 6.1. Study Drug Administered; 6.5. Concomitant Therapy	Text added specifying that the study drug "must be the first anticoagulant administered postoperatively".	Text was needed to clarify the timing of postoperative doses of other anticoagulants in relation to the study drug.
1.1. Synopsis, Safety Evaluations; 1.1. Synopsis, Statistical Methods; 1.3. Schedule of Activities (SoA), Footnote t; 4.1. Overall Design; 8.2. Safety Assessments; 8.3.1. Adverse Events of Interest; 8.3.1.3. Liver Enzyme Elevations and Clinical Liver Events; 9.3.2. Safety Analyses	Changed terminology of Adverse Events of Special Interest to "Adverse Events of Interest".	Terminology changed because for this study expected events and study endpoints are considered adverse events of interest.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis Endpoints; 1.1. Synopsis Pharmacokinetic Evaluations; 1.1. Synopsis Statistical Methods; 3. Objectives and Endpoints; 8.5.3. Pharmacokinetic Parameters and Evaluations; 9.3.3. Other Analyses	For the study endpoints as well as the pharmacokinetic evaluations, the word "level" was removed from the description of JNJ-70033093 exposure.	Exposure level is not a typical description. Therefore, the term "exposure" alone is sufficient as the exposure level is not defined in the protocol.
1.1. Synopsis, Overall Design; 4.1. Overall Design; 6.2. Preparation/ Handling/Storage/ Accountability; 6.4. Study Drug Compliance	Text added noting that selected sites may also use scanning technology to manage clinical study supplies and drug compliance activities. Subjects enrolled at selected sites may use an application on the subject's own smartphone/tablet to confirm study drug administration (JNJ-70033093 capsules only) and receive notifications as per protocol scheduled events (eg, next clinical site visit) as well as additional study information.	Adding pilot program at selected sites to compare manual methods of compliance monitoring, subject retention, end-to-end subject engagement, and drug accountability with an automated method.
1.3. Schedule of Activities (SoA)	• Timing for randomization was changed from Day of surgery -2 to postoperatively, following the primary unilateral elective TKR surgery. In addition, the statement that all subjects must be randomized prior to surgery was removed. • Laboratory samples at the up to Day -30 timepoint were removed. The Factor XI (FXI) antigen required at this time point was also moved to 0 hour. • Specified that enoxaparin may be administered preoperatively 12 hours prior to the surgical procedure in accordance with local standard-of-care. Sites that routinely administer preoperative enoxaparin should continue their standard practice for all study subjects at that site. Per standard-of-care, study drug should not be used for the preoperative dose of enoxaparin for subjects in either treatment group.	As a result of the removal of JNJ-70033093 preoperative dosing, randomization will now be conducted postoperatively because the first dose of study drug will not be administered until 12 to 24 hours after wound closure. In addition, laboratory samples to be collected prior to surgery are no longer necessary since the 0-hour samples will be collected prior to study drug for all subjects. Because randomization will now occur postoperatively, clarification added that 0-hour samples cannot be drawn until after randomization because some are conditional samples based on the treatment group.
1.3. Schedule of Activities (SoA)	Text added to footnote d: Day 4 procedures may be conducted up to +2 days (ie, samples may be drawn on Days 5 or 6) and Day 7 procedures may be conducted +2 days (ie, Day 8 or 9).	Text added to allow flexibility with laboratory testing on weekend days.
1.3. Schedule of Activities (SoA), Footnote e; 6.1. Study Drugs Administered	Text added to clarify that if using the +6-hour window to allow the 12-hour sample to be drawn the following morning, the evening dose of study drug on Day 1 or Day 4 should be administered, but there must be a minimum of 6 hours between doses on these days.	Twice daily dosing should commence at the initiation of treatment and should not be dictated by the pharmacokinetic (PK) sample schedule.
1.1. Synopsis; 1.3. Schedule of Activities (SoA), Footnote q; 6.1. Study Drug Administered	Text added to specify that on the day of the Day 10-14 visit, study drug dosing should occur first thing in the morning, and the PK sample should not be drawn until at least	Text added for clarity on handling of PK samples and dosing.

Section Number and Name	Description of Change	Brief Rationale
	1 hour after the dose is taken. Also added text noting that subjects who discontinue study drug early do not need to have PK sampling conducted at any subsequent visits.	
2.2. Background	Table 1 updated.	Changes reflect the most recent edition of the Investigator's Brochure, Edition 5.
4.1. Overall Design	Modified text to specify the OC may unblind any member of the Steering Committee and that any member unblinded will no longer be involved in the operational aspects of the trial.	Revised to allow the OC flexibility in consulting with the Steering Committee members when discussing data resulting in recommendations to revise the study design.
4.1. Overall Design	Deleted sentence: Pharmacokinetic, PD, and biomarker samples will also be collected and assessed.	Corrected error, since PK/PD samples will not be collected at Week 6.
4.2. Scientific Rationale for Study Design, Choice of Comparator	Clarified text to add that 40-mg daily dose of enoxaparin will be used in this study as it is the dosage regimen used in "most" approved countries for the indication being studied.	Text modified because some countries use enoxaparin 30 mg or 20 mg BID for VTE prophylaxis post TKR surgery.
4.2. Scientific Rationale for Study Design, Choice of Biomarkers	Text changed from postoperatively "at approximately 12 to 24 hours" to "on Day 1 (0 hour) prior to study drug administration".	Text edited to reflect the correct time the cardiac troponins would be drawn postoperatively.
4.3. Justification for Dose	Additional justification provided for using a more conservative approach for the lowest proposed once daily dose based on maintaining pharmacological effect of aPTT prolongation at ≥1.5 times over the full dosing interval.	Additional language needed to justify the lowest proposed once daily dose.
5.1. Inclusion Criteria; 5.3. Lifestyle Considerations	Half-life restrictions for birth control measures were increased by 2 days. The following criteria were updated accordingly: • #8 Requirement for birth control for females was increased from 32 to 34 days • #9 Requirement for egg donation for females was increased from 32 to 34 days • #10 Requirement for birth control for males was increased from 92 to 94 days • #11 Requirement for sperm donation for males was increased from 92 to 94 days	Updated to take a more conservative approach by utilizing the upper end of the JNJ-70033093 half-life for birth control measures. The half-life of JNJ-70033093 as 18 hours versus 11 hours was used and therefore, the 5 half-lives of the study drug increased to 4 days rather than the 2 days previously used.
5.2. Exclusion Criteria	Second bullet from Exclusion Criterion 4 was removed. Exclusion Criterion 5 corrected to state contrast-induced nephropathy instead of neuropathy Exclusion Criterion 8 modified to include sensitivities to heparin and pork products	Exclusion criteria revised for clarity.
5.3. Lifestyle Considerations	The following criterion was modified: #3 Timepoint requirement for the restriction on donating blood was changed from "at least	Lifestyle restriction revised for clarity.

Section Number and Name	Description of Change	Brief Rationale
	4 days after completion of the study" to "until after completion of the study"	
5.4. Screen Failures	Text noting subjects eligible for rescreening only in cases when TKR surgery is rescheduled outside of the 30-day window was removed.	Text was deleted to allow subjects to be rescreened for reasons other than rescheduled surgery.
6.1. Study Drug Administered, Drug Administration	Language added to specify that if a dose of JNJ-70033093 is missed, the capsule should be taken as soon as possible; 2 doses can also be taken together in the evening if the morning dose is missed. No more than 2 doses should be taken in 1 day.	Instructions added to give direction for what to do for a missed dose of JNJ-70033093 study drug.
6.2. Preparation/Handling/ Storage/Accountability	Temperature range for storage of study drug was removed and text was added noting the storage conditions would be specified in the product label.	Text removed for consistency with the product label.
6.5. Concomitant Therapy	Removed text specifying that "in those situations where the study drugs are administered preoperatively, intermittent pneumatic compression is still permitted until the time of the first postoperative dose of the study drug".	Text removed, given that the option for preoperative dosing was removed.
7.2. Subject Discontinuation/Withdrawal From the Study	The last sentence in this section was revised to state that if a subject discontinues study drug and does not withdraw consent, then the subject should continue to have all remaining assessments completed.	Language modified because continuation of remaining study procedures should not be applicable to subjects who withdraw consent.
8. Study Assessments	Blood volume in the table for high-sensitive cardiac troponin T (hs-cTnT) sample is 4.0 mL not 2.7 mL, and the total blood volume was changed from 155.7 to 134.9 mL. Total blood volume collected in the study noted in the table also was corrected (approximately 135 mL, with 95 mL for PD/biomarkers). Total blood volume for subjects randomized to enoxaparin was also added (115 mL) to the text because no PK samples are drawn.	Corrected discrepancy in the volume of laboratory samples between volume of blood to be collected for each subject and the actual volumes of the collection tubes that are supplied by the central laboratory.
8. Study Assessments; 8.2.4. Clinical Safety Laboratory Assessments	The timepoint for collection of the hematology and chemistry laboratory tests and urine sample for urinalysis at screening was removed.	Text revised to align with the sequence of laboratory assessments specified by the central laboratory. In addition, timepoints of hematology and chemistry laboratory tests and urine sample were modified. Screening laboratory testing was removed because preoperative dosing will not be implemented.
8.3.1.3. Liver Enzyme Elevations and Clinical Liver Events	Modified language to clarify the criterion of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥3 times (x) upper limit of normal (ULN), confirmed by repeat is not required to be reported as an adverse event of interest.	Expected reporting of liver enzyme elevations as adverse events of interest clarified. Previous language was unclear, the liver enzyme elevations do not meet the criteria for

Section Number and Name	Description of Change	Brief Rationale
		mandatory adverse event of interest reporting.
8.3.6. Pregnancy	Text edited to note that if a subject becomes pregnant during the study, the subject must be discontinued from further study intervention.	Pregnancy is an exclusion criterion for the study, therefore study drug should be discontinued in the event of pregnancy.
8.4. Treatment of Overdose	Text edited to specify the threshold for reporting an overdose applied to both JNJ-70033093 and enoxaparin and overdose that is considered excessive and medically important by the investigator should be reported as a serious adverse event (medically important event).	Corrected language to include enoxaparin because the protocol text defined the threshold for reporting an overdose of JNJ-70033093 but not enoxaparin.
8.5. Pharmacokinetics	Pharmacokinetic specimen type changed from serum samples to plasma samples.	Correction that PK samples are plasma samples. Typo, wording contains incorrect PK specimen type.
9.1. Sample Size Determination, Table 2	Assumed total VTE rate for 25 mg once daily was deleted and the assumed rate of 24% was added for 50 mg once daily.	Table was updated to reflect the change in planned once daily dosing because it is anticipated that 50 mg once daily, as the lowest once daily dose being tested, would perform at a level equivalent to enoxaparin.
9.2. Populations for Analyses	Week 6 visit was removed from the description of the modified intent-to-treat (mITT) population.	The description for the mITT population revised because subjects will have only 1 valid venography visit at Day 10-14.
9.3.1. Efficacy Analyses	The study objective was modified to add text noting the importance of showing a statistically significant <30% event rate in total VTE in the combined dose group. The text noting that data from preoperative dose regimens will not be used in the modified MCP-Mod analysis and separate analysis was deleted.	The statistical rationale for the study objective was revised for clarity.
9.3.2. Safety Analyses	Edited text to specify that height and weight will be summarized.	Changes in physical examination are not specified in the electronic case report form (eCRF). Any changes in physical examination are evaluated and captured as adverse events as appropriate. Height and weight are recorded in the eCRF.
10.6. Appendix 6/ Definition of Bleeding Events	The description of clinically relevant nonmajor bleeding was revised to indicate a modified version of the criteria from the ADVANCE-2 study, in tandem with clinical judgement, will be used to classify clinically relevant nonmajor bleeding events.	Modified to be in alignment with the standard practice used by the Clinical Events Committee (CEC).

Section Number and Name	Description of Change	Brief Rationale
	Also, the descriptions listed for each bleeding type are examples not criteria. The example of a hematoma was revised to remove “and a drop of hemoglobin is present with no external evidence of bleeding”. The description of minimal bleeding was revised to specify it specifically must be considered a “clinically overt” bleeding event to be included in this category. Moved reference 27, Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. N Engl J Med. 2009;361(6):594-604, from the clinically relevant nonmajor category to the minimal bleeding definition.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

1. PROTOCOL SUMMARY

1.1. Synopsis

A Randomized, Open-Label, Study Drug-Dose Blind, Multicenter Study to Evaluate the Efficacy and Safety of JNJ-70033093 (BMS-986177), an Oral Factor XIa Inhibitor, Versus Subcutaneous Enoxaparin in Subjects Undergoing Elective Total Knee Replacement Surgery

JNJ-70033093 (Bristol-Meyers Squibb Company [BMS]-986177) is a small-molecule therapeutic agent that binds and inhibits the activated form of human coagulation Factor XIa (FXIa) with high affinity and selectivity. It is being codeveloped under a collaboration agreement between BMS and its global affiliates and Janssen Pharmaceutical Research and Development, LLC. JNJ-70033093 is being developed as an orally administered anticoagulant for the prevention and treatment of thromboembolic events (eg, venous thromboembolism [VTE]).

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To determine the efficacy of JNJ-70033093 in preventing total VTE events (proximal and/or distal DVT [asymptomatic confirmed by venography assessment or objectively confirmed symptomatic], nonfatal PE, or any death) during the treatment period.	• Total VTE during the treatment period up to the time of venography as assessed by the CEC. Proof-of-efficacy is reached by either showing a positive dose-response or having less than a 30% total VTE event rate in the combined twice daily (BID) dose group.
Secondary	
• To assess the dose-response of JNJ-70033093 for the occurrence of the endpoint of any bleeding events during the treatment period.	• The composite endpoint of any bleeding event on treatment. Any bleeding will be defined as the composite of major bleeding according to the ISTH criteria modified for the surgical setting, clinically relevant nonmajor bleeding events, or minimal bleeding events as assessed by the CEC.
• To determine the efficacy of JNJ-70033093 in preventing total VTE events during the full study period.	• Total VTE as assessed by the CEC through Week 6.
• To assess the dose-response of JNJ-70033093 for the rate of any bleeding throughout the full study period.	• Occurrence of the composite endpoint of any bleeding events, the composite endpoint of major or clinically relevant nonmajor bleeding events, and the individual components of the composite endpoint of any bleeding as assessed by the CEC through Week 6.

Objectives	Endpoints
• To assess the dose-response of JNJ-70033093 for the prevention of major VTE (death, asymptomatic or symptomatic proximal DVT or PE) during the treatment period and throughout the full study period.	• Major VTE as assessed by the CEC during the treatment period and through Week 6.
• To assess the effect of individual doses of JNJ-70033093 compared with enoxaparin for both efficacy and safety endpoints.	• Total VTE and any bleeding as assessed by the CEC during the treatment period and during the full study period (6 weeks).
• To compare the effect of JNJ-70033093 with enoxaparin for the individual components of the total VTE endpoint.	• All individual components of the primary efficacy endpoint as assessed by the CEC during the treatment period and during the full study period (6 weeks).
• To assess the PK of JNJ-70033093 in men and women undergoing primary unilateral TKR surgery and the relation of these measures to efficacy and safety endpoints (eg, exposure-response analyses).	• Estimation of PK parameters and the effects of demographics and laboratory values (eg, body weight, age, gender, renal function) on the PK of JNJ-70033093. • Estimation of the relationship between JNJ-70033093 exposure with probability of total VTE during the treatment period up to the time of venography and the probability of the composite endpoint of major or clinically relevant nonmajor bleeding events, and the individual components of the composite endpoint of any bleeding event on treatment.
Exploratory	
• To evaluate PD to assess its relationships to PK and the relation of these measures to efficacy and safety endpoints (eg, exposure-response analyses).	• Changes in PD (aPTT, PT, FXI clotting activity, anti-FXa activity, and TGA). • Estimation of the relationship between JNJ-70033093 exposure with the changes in PD.
• To evaluate exploratory biomarkers to assess their relationship to the probability of total VTE during the treatment period.	• Estimation of the changes in biomarkers with the probability of total VTE during the treatment period up to the time of venography and the probability of the composite endpoint of major or clinically relevant nonmajor bleeding events, and the individual components of the composite endpoint of any bleeding event on treatment.

Objectives	Endpoints
• Explore the presence and incidence of asymptomatic MINS as it relates to total knee arthroplasty.	• The presence of an isolated elevated hs-cTnT measurement postoperatively without an alternative explanation (eg, sepsis, atrial fibrillation) in subjects with normal preoperative hs-cTnT. An incremental rise in hs-cTnT without an alternate explanation in individuals with elevated preoperative hs-cTnT.

anti-FXa=anti-Factor Xa; aPTT=activated partial thromboplastin time; BID=twice daily; CEC=Clinical Endpoint Committee; DVT=deep venous thrombosis; FXI=Factor XI; hs-cTnT=high-sensitive cardiac troponin T; ISTH=International Society on Thrombosis and Hemostasis; MINS=myocardial injury in noncardiac surgery; PD=pharmacodynamic; PE=pulmonary embolism; PK=pharmacokinetic; PT=prothrombin time; TGA=thrombin generation assay; TKR=total knee replacement; VTE=venous thromboembolism

Hypothesis

The primary hypothesis is that JNJ-70033093 reduces the risk of total venous thromboembolism (VTE) during the treatment period. This can be achieved by either a statistically significant dose-response trend or an event rate for the combined twice daily (BID) doses of JNJ-70033093 that is statistically lower than 30%. The event rate of 30% is a conservative estimate of the total VTE rate in subjects given placebo.

OVERALL DESIGN

This is an open-label, study drug-dose blind, active-controlled, multicenter, dose-ranging study of JNJ-70033093 in subjects undergoing primary unilateral elective total knee replacement (TKR) surgery. The study uses the prospective, randomized, open-label, blinded endpoint (PROBE) design. Men and women who are ≥50 years of age are eligible to participate if they are considered medically stable and appropriate for anticoagulant prophylaxis as determined by the investigator.

The study will be conducted in 3 phases, which includes an up to 30-day screening phase before surgery, a 10- to 14-day postoperative dosing phase, and a 4-week ±10 days follow-up phase. Unscheduled visits may be performed at the discretion of the investigator for the assessment of any potential bleeding or efficacy endpoint events. The end of study is considered as the last visit for the last subject in the study.

Selected sites may also use scanning technology to manage clinical study supplies and drug compliance activities. Subjects enrolled at selected sites may use an application on the subject's own smartphone/tablet to confirm study drug administration (JNJ-70033093 capsules only) and to receive notifications as per protocol scheduled events (eg, next clinical site visit) as well as additional study information.

An Operations Committee (OC), Steering Committee, and independent Clinical Events Committee (CEC) will be commissioned for this study. The OC will be unblinded, the Steering Committee will be blinded to the dose and frequency of JNJ-70033093, and the CEC will be blinded to both the study drug and the dose. The OC will be responsible for reviewing ongoing safety and efficacy data by unblinded subject treatment assignments approximately every 3 to 8 weeks on a periodic basis.

Unblinded periodic and interim analyses will be conducted by the OC for the purposes of safety oversight and as part of the adaptive approach. The first interim analysis will be triggered when approximately 300 subjects (approximately 50 subjects in each of the JNJ-70033093 BID treatment groups) have completed venography or have had a symptomatic VTE event. Both periodic and the interim analyses results will be used to guide the decision to drop a dose of JNJ-70033093 and/or readjust the randomization ratio. The number of subjects who were planned to be randomized into the dropped dosing

regimen can be allocated to one of the other dosing groups. The interim analysis will also serve as the formal venue to assess study status and possibly add once daily 50 or 200 mg dose of JNJ-70033093 based on available efficacy and safety data. If pharmacokinetic/pharmacodynamic (PK/PD) analysis results are available at the time of the interim analysis, the results will be included in the review.

Additional interim analyses will be conducted, as needed, at the discretion of the OC.

NUMBER OF SUBJECTS

A target of 900 subjects will be randomly assigned to treatment in this study, with an option to increase the randomization target to approximately 1,200 subjects based on the possible addition of once daily dose groups, and/or the evaluability rate. The number of subjects who were planned to be randomized into the dropped dosing regimen can be allocated to one of the other dosing groups.

STUDY DRUG GROUPS AND DURATION

Eligible subjects will be randomly assigned to treatment with either JNJ-70033093 or enoxaparin postoperatively following unilateral elective TKR surgery. Subjects will know the treatment to which they were assigned but subjects randomly assigned to JNJ-70033093 will remain blinded to the dose and frequency (ie, BID versus once daily).

First dosing of both study drugs will occur while the subject is still hospitalized, with administration beginning a minimum of 12 hours and a maximum of 24 hours after the end of TKR surgery, which is defined as the time of wound closure, and must be the first anticoagulant administered postoperatively.

Enoxaparin may be administered preoperatively 12 hours prior to the surgical procedure in accordance with local standard-of-care. Sites that routinely administer preoperative enoxaparin should continue their standard practice for all study subjects at that site. Per standard-of-care, study drug should not be used for the preoperative dose of enoxaparin for subjects in either treatment group.

Following discharge or transfer to an alternate facility, subjects will continue to take the assigned study drug for a total of 10 to 14 days. Unilateral venography assessment of the operated leg will be performed within 1 calendar day after the last dose of either JNJ-70033093 or enoxaparin is taken. Study visits should be conducted in the morning, when possible study drug dosing should not occur until after the pharmacokinetic (PK) sample has been drawn. On the day of the Day 10-14 visit, study drug dosing should occur first thing in the morning, and the PK sample should not be drawn until at least 1 hour after the dose is taken.

The total duration of participation following randomization will be approximately 6 weeks.

Each subject randomly assigned to JNJ-70033093 will take 4 capsules a day, 2 capsules in the morning and 2 capsules in the evening at approximately the same time each day, as follows:

Group A: JNJ-70033093 25 mg BID (1 capsule JNJ-70033093 25 mg and 1 placebo capsule, BID)

Group B: JNJ-70033093 50 mg BID (2 capsules JNJ-70033093 25 mg BID)

Group C: JNJ-70033093 100 mg BID (1 capsule JNJ-70033093 100 mg and 1 placebo capsule, BID)

Group D: JNJ-70033093 200 mg BID (2 capsules JNJ-70033093 100 mg BID)

Group E: JNJ-70033093 25 mg once daily (1 capsule JNJ-70033093 25 mg and 1 placebo capsule in the morning and 2 placebo capsules in the evening). Enrollment in this group discontinued per Amendment 1. Subjects randomized to this group prior to Amendment 1 will complete study procedures.

Group F: JNJ-70033093 200 mg once daily (2 capsules JNJ-70033093 100 mg in the morning and 2 placebo capsules in the evening). Enrollment in Group F suspended per Amendment 1 and may become

optional depending on OC decision. Subjects randomized to this group prior to Amendment 1 will complete study procedures.

Group G: JNJ-70033093 50 mg once daily (2 capsules JNJ-70033093 25 mg in the morning and 2 placebo capsules in the evening) Enrollment in Group G will become optional per Amendment 1.

Subjects randomly assigned to JNJ-70033093 who take the first dose of study drug on the evening of surgery should take the 2 capsules assigned to the Day 1 morning dose (left side of blister card). On subsequent days the first dose should always be the left 2 capsules and the evening dose should be the 2 capsules on the right.

Subjects randomly assigned to enoxaparin (Group I) will take a subcutaneous (SC) dose of enoxaparin 40 mg once daily, supplied as a prefilled syringe.

EFFICACY EVALUATIONS

Efficacy evaluations will include unilateral venography assessment of the operated leg and assessments of symptomatic deep vein thrombosis (DVT), pulmonary embolism (PE), or death to assess the primary, secondary, and exploratory efficacy outcomes.

PHARMACOKINETIC EVALUATIONS

Plasma samples will be analyzed to determine concentrations of JNJ-70033093 using a validated, specific, and sensitive (eg, liquid chromatography-mass spectrometry/mass spectrometry) method by or under the supervision of the sponsor. Pharmacokinetic samples will be collected from all subjects randomly assigned to JNJ-70033093.

In addition, residual plasma PK samples may be stored for future analysis of the metabolite profile, if needed.

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters (eg, apparent clearance, apparent volume of distribution) and exposure for exposure-response analysis of JNJ-70033093 and associated variables will be derived using population PK modeling.

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Venous blood samples will be collected for pharmacodynamic (PD) evaluation of aPTT, PT, Factor XI (FXI) clotting activity, anti-Factor Xa (anti-FXa) activity, thrombin generation assay (TGA), and biomarker evaluation (D-dimer, high-sensitive cardiac troponin T [hs-cTnT], and FXI antigen). Factor XI clotting activity will be assessed in subjects randomly assigned to JNJ-70033093 and anti-FXa activity will be assessed in subjects randomly assigned to enoxaparin. Subjects who experience a suspected major and clinically relevant nonmajor bleeding event or symptomatic VTE should have PD samples collected as soon as practically possible after the event occurs.

Blood samples will also be collected and a plasma sample archived for future exploratory PD research related to the safety and/or efficacy of JNJ-70033093.

SAFETY EVALUATIONS

The safety and tolerability of JNJ-70033093 will be evaluated throughout the study by the assessment of adverse events, including serious adverse events, adverse events of interest (ie, bleeding events, liver enzyme elevations and clinical liver events, and wound or joint complications), clinical laboratory tests (ie, hematology, clinical chemistry, urinalysis), and physical examination. Safety evaluations may be performed at unscheduled timepoints, if deemed by the investigator or appropriate designee as necessary to ensure the safety of the subject. All suspected symptomatic efficacy events (VTE) will also be captured as adverse events of interest.

STATISTICAL METHODS

Assuming the evaluability rate (rate of subjects with a valid assessment of potential efficacy outcome and who take a least 1 dose of study drug) is 80%, if the true underlying total VTE event rates are as projected, the study is expected to have over 99% power to declare proof-of-efficacy at a 1-sided, 5% α-level. Proof-of-efficacy is defined as either a statistically significant dose-response trend or primary endpoint event rate for the combined BID JNJ-70033093 groups that is statistically lower than 30%. The exact power will vary because of the nature of the adaptive study design.

Comparison with enoxaparin will be based on the comparison between the highest dose of JNJ-70033093 with acceptable safety and enoxaparin. For example, if the highest dose of JNJ-70033093 with acceptable safety is 200 mg BID, the number of evaluable subjects at this dose and enoxaparin groups is expected to be 120 and 240 subjects respectively, the power to detect a statistically significantly lower total VTE event rate against enoxaparin, at 1-sided, 5% α-level, is over 90%.

The study objectives include proof-of-efficacy and estimation of dose-response relationship in total VTE. The dose-response trend and estimation of the dose-response relationship will be addressed by a unified (modified) multiple comparison procedures and modeling (MCP-Mod) approach, utilizing collective data from postoperative regimens.

The intent-to-treat (ITT) population will include all randomized subjects who have signed an informed consent. The modified intent-to-treat (mITT) population will be a subset of the ITT population consisting of subjects with a valid assessment of potential efficacy outcome and who take at least 1 dose of the study drug. The primary analyses of efficacy endpoints will be based on CEC-adjudicated events from the mITT population. The primary efficacy endpoint and its components will be summarized by dose and treatment group.

All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summaries, listings, or subject narratives will be provided, as appropriate, for those subjects who die, who discontinue the study drug due to an adverse event, or who experience a severe or a serious adverse event.

Adverse events of interest that will be counted or listed are bleeding events, wound or joint complications, and liver enzyme elevations and clinical liver events.

The safety population will be a subset of the ITT population consisting of subjects who take at least 1 dose of the study drug. The analyses of bleeding adverse events will be based on the CEC-adjudicated events; all other nonefficacy or nonbleeding adverse events will be based on investigator-reported events in the safety population.

Estimation of the dose-response relationship in any bleeding will be addressed by a unified (modified) MCP-Mod approach as with efficacy. Any bleeding, major bleeding, clinically relevant nonmajor bleeding, composite of major or clinically relevant nonmajor bleeding, and minimal bleeding will be summarized by the dose and treatment group.

Laboratory data will be summarized by type of laboratory test.

Population PK analysis of plasma concentration-time data of JNJ-70033093 will be performed using nonlinear mixed-effects modeling. Data will be listed for all subjects with available plasma concentrations per treatment group.

For each treatment group, descriptive statistics, including arithmetic mean, standard deviation (SD), coefficient of variation, median, minimum, and maximum will be calculated for all individual derived

PK parameters including exposure information of JNJ-70033093. Descriptive statistics will be used to summarize JNJ-70033093 plasma concentrations at each sampling time point. Exposure-response analyses will be conducted to explore the relationship of the plasma concentration of JNJ-70033093 with efficacy and safety endpoints.

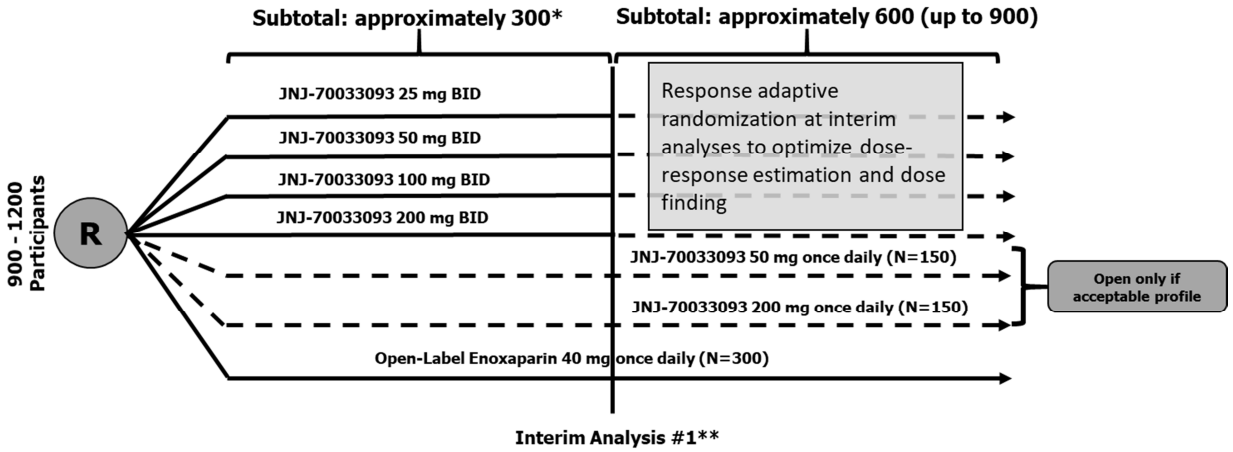
Descriptive statistics, including mean, median, SD, minimum, and maximum will be provided for the percent change from baseline of the PD (activated partial thromboplastin time [aPTT], prothrombin time [PT], FXI clotting activity, anti-FXa activity, thrombin generation assay [TGA]) and biomarker (D-dimer, hs-cTnT) parameters by nominal time of collection and dose and regimen level. The parameters may be statistically analyzed using mixed models. FXI antigen levels will be summarized.

The relationship between observed plasma concentration of JNJ-70033093 and measured PD markers will be investigated graphically. If appropriate, PK/PD exposure and response relationships may be further analyzed quantitatively.

The relationship between the plasma PK exposure of JNJ-70033093 derived from the population PK model will be correlated with the measured PD markers and safety/efficacy endpoints via graphical analysis.

1.2. Schema

Figure 1: Schematic Overview of the Study



Study drug-dose blind design: Treatment with enoxaparin or JNJ-70033093 will be open-label but blinded to study drug dose and regimen for all subjects randomized to JNJ-70033093. All subjects will receive study drug for 10 to 14 days of randomized treatment, followed by unilateral venography and a follow-up study visit at Week 6.

*** Interim Analysis to be conducted when approximately 50 subjects in each of the BID treatment groups have completed the venography or have had a symptomatic VTE event.**

**** Additional interim analyses will be conducted, as needed, at the discretion of the Operations Committee (OC). These decisions will be made only after taking the safety and efficacy profiles of JNJ-70033093 into account.**

1.3. Schedule of Activities (SoA)

Phase	Screening[a]		Postoperative Dosing Phase											Follow-up[b]	
			Day 1[c]					Day 4[d]							
Study Procedures	Pre-operative (up to Day -30)	Randomization (postoperative)	0h	2h	4h	12h[e]	Day 2	0h	2h	4h	12h[e]	Day 7[d]	Day 10-14 (EOD/EW)[f]	Week 6 (±10 days)	Unscheduled Visit[g]
Screening/Baseline															
Informed consent[h]	X														
Inclusion/exclusion criteria[i]	X	X													
Medical history and demographics	X														
Bleeding risk history	X														
Relevant prestudy therapy	X														
Urine or serum pregnancy test (WOCBP only)	X[j]	X											X		
TKR surgery[k]		X													
Study Drug Administration															
Randomization		X													
Dispense/administer study drug[l]		X	X[l]			X	X	X			X	X	X[l]		
Drug accountability													X		
Safety Assessments															
Physical examination[m]	X												X	X	
Efficacy Assessments															
Venography of the operated leg													X[n]		
Symptomatic VTE[o]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments															
Hematology			X[p]				X						X	X	
Serum chemistry			X[p]				X						X	X	
Urinalysis			X[p]										X	X	
Pharmacokinetics															
PK sample collection[q]				X	X	X	X	X	X	X	X	X	X		X
Pharmacodynamics/ Biomarker															
aPTT, PT, and TGA			X[p]	X[r]	X[r]		X[r]	X[r]		X[r]			X		X

Phase	Screening[a]		Postoperative Dosing Phase											Follow-up[b]	
			Day 1[c]					Day 4[d]							
Study Procedures	Pre-operative (up to Day -30)	Randomization (postoperative)	0h	2h	4h	12h[e]	Day 2	0h	2h	4h	12h[e]	Day 7[d]	Day 10-14 (EOD/EW)[f]	Week 6 (±10 days)	Unscheduled Visit[g]
FXI clotting activity, anti-FXa activity, and archive sample[s]			X[p]		X								X		X
FXI antigen			X[p]												
hs-cTnT			X[p]										X		
D-dimer			X[p]										X	X	
Ongoing Subject Review															
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events monitoring[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

anti-FXa=anti-Factor Xa; aPTT=activated partial thromboplastin time; EOD=end of dosing; EW=early withdrawal; FXI=Factor XI; h=hour; hs-cTnT=high-sensitive cardiac troponin T; PK=pharmacokinetic; PT=prothrombin time; TGA=thrombin generation assay; TKR=total knee replacement; WOCBP=women of childbearing potential

[a] Screening for eligible subjects will be performed within and including 30 days before administration of the first dose of postoperative study drug. Final eligibility must be confirmed after surgery and prior to randomization.

[b] Reasonable attempts should be made to conduct the follow-up visit(s) at the scheduled time points. If a subject withdraws from the study before the end of the follow-up phase and is unwilling or unable to return for follow-up visits in person or have follow-up contacts, the study-site should collect as much follow-up visit information as possible, including contacting the subject or subject's representative or health care professional by telephone or mail.

[c] All study days will be counted from the first postoperative day of dosing (ie, Day 1). The subject's clinical status and appropriateness for anticoagulation must be checked again before first dose of postoperative study drug.

[d] Study procedures will be conducted on Days 4 and 7 only for those subjects who are still hospitalized. Day 4 procedures may be conducted up to +2 days (ie, samples may be drawn on Days 5 or 6) and Day 7 procedures may be conducted +2 days (ie, Day 8 or 9).

[e] Assessments may be conducted at 12 hours ±6 hours. In addition, the 12-hour samples on Day 1 and Day 4 should be drawn before administering the next scheduled dose of study drug. If using the +6-hour window to allow the 12-hour sample to be drawn the following morning, the evening dose of study drug on Day 1 or Day 4 should be administered, but there must be a minimum of 6-hours between doses on these days.

[f] Subjects who prematurely discontinue study drug (ie, EW) before the end of the postoperative dosing phase will be instructed to return to the study-site at the originally scheduled Day10-14 visit to conduct assessments, including the venography of the operated leg (unless a pulmonary embolism [PE] or symptomatic proximal deep vein thrombosis [DVT] has been diagnosed), and to complete the remaining visits through the Week 6 assessments.

[g] At the discretion of the investigator, subjects may return to the study-site between scheduled visits. Subjects should return to the study-site for the assessment of any potential bleeding or efficacy endpoint events. Unscheduled PK and pharmacodynamic (PD) samples should be collected as soon as practically possible for any subject who experiences a suspected symptomatic thrombotic or bleeding event.

[h] Must be signed before first study-related activity and before TKR surgery. At the time of informed consent, 2 alternative means of contact for each subject will be collected (eg, contact information of the subject's children, spouse, significant other, caretaker, legal representative, health care professional).

[i] The investigator will need to determine if the subject is medically appropriate for anticoagulant prophylaxis on the basis of physical examination, medical history, and clinical laboratory tests performed as part of screening for elective TKR surgery. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documents in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

[j] Pregnancy testing to be done within 2 days of the first dose of study drug.

[k] Details regarding the TKR surgery and the post-surgery management (eg, type of anesthesia, procedure duration, cement use, tourniquet use and duration, drain use and volume, use of all mechanical venous thromboembolism [VTE] prophylaxis methods) will be collected in the electronic case report form (eCRF).

[l] All subjects will receive the first postoperative dose (JNJ-70033093 or enoxaparin) while the subject is still hospitalized, with administration beginning a minimum of 12 hours and a maximum of 24 hours after the end of the TKR surgery, defined as the time of wound closure, and must be the first anticoagulant administered postoperatively. Enoxaparin may be administered preoperatively 12 hours prior to the surgical procedure in accordance with local standard-of-care. Sites that routinely administer preoperative enoxaparin should continue their standard practice for all study subjects at that site. Per standard-of-care, study drug should not be used for the preoperative dose of enoxaparin for subjects in either treatment group. Subjects randomly assigned to JNJ-70033093 who take the first dose of study drug on the evening of surgery should take the 2 capsules assigned to the Day 1 morning dose (left side of blister card). On subsequent days the first dose should always be the left 2 capsules and the evening dose should be the 2 capsules on the right. Subjects will be given a supply of study drug at the time of discharge or transfer to an alternate facility, with instructions to take the study drug, at approximately the same time each day for 10 to 14 days.

[m] Height and weight should be obtained at the screening visit, with weight only at the final visit. Wounds will be assessed at all visits as part of the adverse event assessment.

[n] Subjects who complete dosing will return to the study-site for final EOD assessments (at the Day 10-14 visit), at which time unilateral venography of the operated leg will be performed within 1 calendar day after the last dose of either JNJ-70033093 or enoxaparin is taken. If dosing is prematurely discontinued, the venography should be completed on the originally scheduled Day 10-14 (EOD) visit, not earlier. If a subject has suspected symptomatic DVT prior to the Day 10-14 visit, an ultrasound will be performed. In these cases, if the ultrasound confirms symptomatic proximal DVT, a subsequent venography assessment is not required. If the ultrasound is negative or confirms a distal DVT, the venography assessment should be conducted on the Day 10-14 visit. In addition, if the subject is objectively diagnosed with a PE meeting the specified definitions prior to Day 10-14, a subsequent venography assessment of the operated leg is not required.

[o] Suspected symptomatic VTE (DVT, PE, death) will be reported by the investigator and reviewed by the Clinical Events Committee (CEC) to ascertain if a thrombotic event has occurred.

[p] The baseline laboratory assessments, including PD and biomarkers, may be taken at any time on Day 1, after randomization and before the first dose of study drug.

[q] All sites will collect PK blood samples for subjects randomly assigned to JNJ-70033093 at all visits up to Day 10-14. The Day 1 and Day 4 samples will be drawn at approximately 2, 4, and 12 hours after the first oral dosing of that day. The Day 2 blood sample will be drawn before the first dose of study drug on Day 2 and may be done with the subject as an inpatient or outpatient. The Day 7 sample will be drawn approximately 12 hours after the previous dose. Study visits should be conducted in the morning, when possible. Study drug dosing should not occur until after the PK sample has been drawn. On the day of the Day 10-14 visit, study drug dosing should occur first thing in the morning, and the PK sample should not be drawn until at least 1 hour after the dose is taken. For subjects who discontinue study drug early PK sampling does not need to be conducted at any subsequent visits.

[r] Pharmacodynamic samples are optional for subjects randomized to enoxaparin.

[s] Factor XI clotting activity will be assessed in subjects randomly assigned to JNJ-70033093 and anti-FXa activity will be assessed in subjects randomly assigned to enoxaparin. Archive samples will be collected from all subjects at these timepoints.

[t] All adverse events will be reported from the time a signed and dated informed consent form (ICF) is obtained until the completion of the subject's last study-related procedure, including all adverse events of interest (ie, bleeding events, liver enzyme elevations and clinical liver events, and wound or joint complications). All suspected symptomatic efficacy events (VTE) will also be captured as adverse events of interest.

2. INTRODUCTION

JNJ-70033093 (Bristol-Meyers Squibb Company [BMS]-986177) is a small-molecule therapeutic agent that binds and inhibits the activated form of human coagulation Factor XIa (FXIa) with high affinity and selectivity. It is being codeveloped under a collaboration agreement between BMS and its global affiliates and Janssen Pharmaceutical Research and Development, LLC. JNJ-70033093 is being developed as an orally administered anticoagulant for the prevention and treatment of thromboembolic events (eg, venous thromboembolism [VTE]).

JNJ-70033093 is expected to provide noninferior or superior efficacy with reduced bleeding risk versus active comparators. Evidence to support this target profile includes the following:

- Congenital deficiency of Factor XI (FXI) appears to provide protection from both arterial and venous thrombotic events and is rarely associated with unprovoked major bleeding (ie, less bleeding than with other factor deficiencies like Factor X).[18]
- Knockout mice with essentially no FXI develop normally, are resistant to both venous and arterial thrombosis, and do not have any spontaneous bleeding.[37]
- A Phase 2 study in subjects undergoing total knee replacement (TKR) with preoperative dosing of a FXI antisense oligonucleotide (ASO) that resulted in >80% reduction in FXI levels demonstrated superior efficacy compared with enoxaparin 40 mg once daily (total VTE 4% [95% confidence interval {CI}: 1, 12] vs 30.0% [95% CI: 20, 43], p<0.001) with numerically less major or clinically relevant nonmajor bleeding events (3% [95% CI: <1, 9] vs 8% [95% CI: 3, 17], p=0.16).[4]

For the most comprehensive nonclinical and clinical information regarding JNJ-70033093, refer to the latest edition of the Investigator's Brochure (IB) for JNJ-70033093.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

2.1. Study Rationale

This study will evaluate the efficacy and safety of JNJ-70033093 in a TKR population. Data from this study will be used, in part, to define the therapeutic window of this FXIa-inhibitor. Results from this study will be used to develop Phase 3 studies in subjects requiring anticoagulation, including a possible indication of VTE prevention in subjects undergoing orthopedic procedures.

2.2. Background

Nonclinical Studies

JNJ-70033093 is a high affinity, direct, small-molecule inhibitor of human coagulation FXIa, with an inhibition constant (K_i) of 0.11 nM. JNJ-70033093 has >5,000-fold selectivity for FXIa over other blood coagulation proteases and structurally related enzymes involved in digestion, fibrinolysis, and inflammation, except chymotrypsin and plasma kallikrein where the K_i values are 35 nM and 44 nM, respectively. Human deficiency of plasma prekallikrein is tolerated

without a known phenotype. The protein digestive function of chymotrypsin in the intestine is partially redundant with trypsin. Based on these observations, it is not expected that inhibition of chymotrypsin or plasma kallikrein activity will be a safety concern. To date, nonclinical toxicological studies have not shown any issues attributable to inhibition of either of these enzymes. In standard plasma coagulation assays, JNJ-70033093 produced concentration-dependent increases in activated partial thromboplastin time (aPTT), but not prothrombin time (PT), indicating a selective effect on the intrinsic pathway. In the in-vitro thrombin generation assay (TGA) using human platelet-rich plasma, JNJ-70033093 (0.1 – 10 μM) increased the lag time and time to peak, while reducing peak thrombin and endogenous thrombin potential. In the thromboelastography assay using human whole blood, JNJ-70033093 produced a concentration-dependent increase in the reaction time but did not affect the maximum amplitude. Consistent with its mode of action, JNJ-70033093 did not have any direct effect on platelet aggregation induced by adenosine diphosphate, collagen, or arachidonic acid in human platelet-rich plasma in-vitro. Evaluations of the antithrombotic and antihemostatic effects of intravenous (IV) JNJ-70033093 infusions were performed in anesthetized rabbits. JNJ-70033093 caused dose-dependent inhibition of thrombosis formation in injured arteries. In this experiment, the JNJ-70033093 plasma concentrations required to reduce thrombus weight by 20% and 50% were 34.5 ng/mL (55 nM) and 235 ng/mL (375 nM), respectively. In the same model, JNJ-70033093 also restored blood flow to an artery partially occluded by a preexisting thrombus. In this experiment, the JNJ-70033093 plasma concentration required to reduce thrombus weight by 50% was 665 ng/mL (1,060 nM). JNJ-70033093 did not increase bleeding times in rabbits, even at doses that produced approximately 80% inhibition of thrombus formation. The combination of JNJ-70033093, at a dose that produces approximately 80% inhibition of thrombus formation, and aspirin, at a dose that increases bleeding time by approximately 2-fold, did not lead to increased bleeding in rabbits over aspirin treatment alone. Additional rabbit cuticle bleeding-time studies were conducted with JNJ-70033093 in combination with clopidogrel and aspirin. However, off-target effects due to thrombin inhibition (as observed by a 1.8-fold increase in ex-vivo thrombin time coagulation assay) at these high drug exposures observed in rabbits confounded the interpretation of those studies.[21]

Safety Pharmacology

JNJ-70033093, at maximum-tested concentrations of 15.66 to 93.97 μg/mL (serum/protein free), did not exhibit substantial off-target activity against a panel of 42 targets that included G-protein coupled receptors, monoamine neurotransmitter transporters, ligand-gated and non-ligand-gated ion channels, nuclear hormone receptors, or selected enzymes (acetylcholinesterase, monoamine oxidase, and phosphodiesterase). In in-vitro studies, JNJ-70033093 inhibited cardiac human ether-a-go-go gene/rapidly activating delayed rectifier potassium current (hERG/IKr) potassium channel currents, with a concentration at which 50% inhibition was observed (IC_{50}) of 4.2 μg/mL (6.7 μM; 33 times [x] and 14x the projected free/unbound maximum plasma concentration [C_{max}] in humans at 200 mg once daily and twice daily [BID], respectively). At 6.26 μg/mL (10 μM), JNJ-70033093 had minimal effects on cardiac sodium channel currents (22.9% to 25.3% inhibition at 1 and 4 Hz, respectively) and calcium channel currents (13.9% inhibition).[21]

In an exploratory study in anesthetized rabbits, JNJ-70033093 was associated with decreased blood pressure (up to -14.1% pretest) and increased heart rate (up to +20.9% pretest) at plasma concentrations ≥5.7 μg/mL, with prolonged QT interval corrected for heart rate using Fridericia's formula (by ~6.5 ms) also noted at 19.61 μg/mL (13x and 5.5x the projected C_{max} at 200 mg once daily and BID, respectively. In a non-Good Laboratory Practice telemetry study in rats, there were minimal increases in blood pressure (≤5%) at C_{max} ≥5.0 μg/mL and heart rate (≤6%) at C_{max} of 16.14 μg/mL. These rabbit and rat findings were considered nonadverse due to their small magnitude. Importantly, in conscious monkeys, no JNJ-70033093-related hemodynamic or electrocardiogram changes were identified at any dose tested in 2 telemetry studies (C_{max} ≤5.46 μg/mL) or 3 repeat-dose toxicity studies after approximately 2 weeks (C_{max} ≤21.2 μg/mL, electrocardiogram not assessed), 6 weeks (C_{max} ≤7.24 μg/mL), and 9 months (C_{max} ≤6.56 μg/mL) of dosing. The exposure at the no observed adverse effect level (NOAEL) in the 9-month monkey study was 4.3x and 1.8x the projected C_{max} in humans at 200 mg once daily and BID, respectively. Taken together, the in-vitro and in vivo data indicate low potential of JNJ-70033093 for cardiovascular effects in humans.[21]

Toxicology

The nonclinical safety profile of JNJ-70033093 has been evaluated in a comprehensive battery of in-vitro studies and in vivo toxicity studies mainly in rats and monkeys. JNJ-70033093 has a high affinity for human FXIa (K_i = 0.11 nM) and cynomolgus monkey FXIa (K_i = 0.15 nM), but has a very weak affinity for rat FXIa (K_i = 490 nM). As such, the rat was chosen for evaluation of potential off-target toxicity, and the monkey was chosen as a non-rodent species to assess both on-target as well as off-target toxicity.

The scope of the toxicology evaluations, as summarized below, supports continued testing of JNJ-70033093 in humans. Unless otherwise specified, exposure multiples at NOAELs and pertinent findings in toxicology studies are expressed relative to the projected exposures at 200 mg once daily (C_{max} of 1.512 μg/mL and area under the concentration versus time curve from 0 to 24 hours of the last measurable concentration [AUC_{0-24h}] of 14.634 μg•h/mL) and 200 mg BID (C_{max} of 3.579 μg/mL and AUC_{0-24h} of 60.514 μg•h/mL), the highest once daily and BID doses proposed for the Phase 2 study.

The protein binding for of JNJ-70033093 is comparable in rat, monkey, and human sera (97.1%, 89.1%, and 91.5%, respectively). As such, the exposure multiples have not been corrected for free fraction and are expressed as ratios of total exposure unless otherwise specified.

JNJ-70033093 was nongenotoxic in-vitro (Ames and cytogenetics assays, tested at maximum concentrations required by the International Council for Harmonisation [ICH] guidelines) and in vivo (micronucleus assessment; conducted as part of a 6-week toxicity study) in rats at doses up to 200 mg/kg/day (AUC_{0-24h} of 319 μg·h/mL; 22x and 5.3x the projected exposure in humans at 200 mg once daily and BID, respectively). Likewise, BMT 210370, an aniline metabolite of JNJ-70033093, was negative in the exploratory assays for mutagenicity and clastogenicity.[21]

In definitive embryo-fetal development studies,[21] JNJ-70033093 was neither embryo-fetal lethal or teratogenic. The exposures at the developmental NOAEL were 11x and 2.7x in rats (166 μg·h/mL) and 4.7x and 1.1x in rabbits (68.4 μg·h/mL) relative to the projected human area under the plasma concentration-time curve (AUC) at 200 mg once daily and BID, respectively.

JNJ-70033093 was well tolerated by rats at all doses tested for 2 and 6 weeks (10, 50, and 200 mg/kg/day) and for 6 months (10, 30, and 50 mg/kg/day).[21] Relative to Day 1 values, AUC exposures to JNJ-70033093 were decreased following repeated dosing. This finding was rat specific, noted in both sexes (with greater effects in males), and most evident in the 6-month study (with Week-26 AUCs 0.3x in males and 0.5x to 0.6x in females, relative to Day-1 values). Other noteworthy findings in rats were limited to increased serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or glutamate dehydrogenase at ≥50 mg/kg/day in the subchronic studies and at ≥10 mg/kg/day in the 6-month study. These findings were considered nonadverse due to their minimal to mild magnitude, transient and/or non-progressive nature with continued dosing, lack of concurrent increases in serum bilirubin suggestive of altered liver function, full reversibility upon dosing cessation, and absence of microscopic evidence of liver injury. The NOAEL in the 6-month study was 50 mg/kg/day and the associated AUC values at Week 26 (26.1 μg•h/mL in males and 96.3 μg•h/mL in females) were ≤6.6x and ≤1.6x the projected exposures in humans at 200 mg once daily and BID, respectively.

JNJ-70033093 was clinically well tolerated by monkeys at all doses tested for 2 weeks (10, 50, and 150 mg/kg/day), 6 weeks (5, 15, and 50 mg/kg/day), and 9 months (10, 30, and 50 mg/kg/day).[21] There was no substantial accumulation or loss of exposures after repeated dosing. Consistent with the intended pharmacology of JNJ-70033093, exposure-dependent prolongations of aPTT were noted at ≥10 mg/kg/day across all studies. At 50 mg/kg/day in the 2-week and 9-month studies, there were also accompanying increases in PT in some monkeys. Overall, the increased aPTT and PT were considered nonadverse as they were not associated with clinical or microscopic signs of bleeding and were fully reversible after cessation of dosing. Additional JNJ-70033093-related changes in monkeys were limited to decreases in red blood cell parameters and serum albumin at ≥50 mg/kg/day in the 2-week study and were considered adverse only in 1 female at 50 mg/kg/day with very high JNJ-70033093 exposure (AUC of 540 μg•h/mL). As such, the high dose in the subsequent 6-week and 9-month studies was capped at 50 mg/kg/day. Based on the absence of adverse findings at any dose tested, the high dose of 50 mg/kg/day was considered the NOAEL for the 9-month study and the associated AUC (76.2 μg•h/mL at Week 39) was 5.2x and 1.3x the projected exposure in humans at 200 mg once daily and BID, respectively.

Collectively, the results of nonclinical toxicology studies demonstrated an acceptable safety profile and support the use of JNJ-70033093 in humans at doses up to 200 mg BID.

Pharmacokinetic Profile

The pharmacokinetic (PK) characteristics of JNJ-70033093 were evaluated in rats, rabbits, dogs, and monkeys after IV and oral dosing.[21] The absolute oral bioavailability of JNJ-70033093 was 18% and 32% in rats and monkeys, respectively. JNJ-70033093 was a substrate of human efflux

transporters including P-glycoprotein (P-gp). After IV administration, the terminal elimination half-life was short (1.4, 2.5, 4.0, and 2.7 hours in rats, rabbits, dogs, and monkeys, respectively) and the total plasma clearance was low in all the species (9% to 23% of the reported liver blood flow). JNJ-70033093 distributed extravascularly in animals. Serum protein binding was 91.5% in human, and 89.1% to 97.1% in animals. Uptake studies with human hepatocytes suggested that active transport processes are at least partially involved in the hepatic uptake of JNJ-70033093. Further studies with rifamycin SV (an organic anion-transporting polypeptide [OATP] inhibitor) suggested that OATPs are not involved in the hepatic uptake of JNJ-70033093 (confirmed in a clinical drug-drug interaction (DDI) study [CV010014]).[21].

In-vitro, JNJ-70033093 was the predominant drug-related compound (representing 94% to 99% of total drug-related ultraviolet [UV] peak area) in incubations with liver microsomes or hepatocytes. No unique metabolite was observed in human hepatocyte or microsome incubates. In rats, intact monkeys, and monkeys from a cholecystocentesis study, following a single oral dose of 200-, 150-, and 30-mg/kg, respectively, JNJ-70033093 was the predominant drug-related compound detected in plasma (approximately 99%, 87.2%, and 90.8% of total drug-related UV peak area at C_{max}, respectively). In rats and monkeys, several metabolites were detected including an aniline containing metabolite, Met 17 (BMT 210370), which represented 6% to 36% of the AUC of JNJ-70033093 in monkey, but was present at very low levels in rat plasma (metabolite was nongenotoxic as described later). In monkeys from the cholecystocentesis study, numerous metabolites were detected in bile including BMT 210370. No glutathione conjugate was detected in-vitro or in vivo. In bile duct-cannulated rats and monkeys, orally administered [^{14}C] JNJ-70033093 was cleared primarily through biliary elimination.[21] In dogs and monkeys, following IV doses of 0.5 mg/kg, urinary excretion was found to be a minor route of elimination.

Cytochrome P450 (CYP) 3A4/5 was identified as the primary enzyme responsible for the oxidative metabolism of JNJ-70033093. The potential DDIs with CYP3A inhibitors were confirmed in a clinical DDI study. JNJ-70033093 exhibited little or no reversible and time-dependent inhibition of the CYPs. JNJ-70033093 did not inhibit uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzyme (IC_{50} ≥20 μM or 12.5 μg/mL). Relative to the C_{max} values of JNJ-70033093 in humans (6.09 μM or 3.8 μg/mL after 200-mg BID doses), JNJ-70033093 showed low potential to induce the CYP1A2, CYP2B6, or CYP3A4 messenger ribonucleic acid levels in primary human hepatocytes (absence of CYP3A induction confirmed in a clinical DDI study).

JNJ-70033093 was a substrate of P-gp, but not of organic anion transporter (OATPs). JNJ-70033093 inhibited breast cancer resistance protein (IC_{50}=19.6 μM or 12.3 μg/mL), OATP1B1 (IC_{50}=4.8 μM or 3.0 μg/mL), OATP1B3 (IC_{50}=9.7 μM or 6.1 μg/mL), sodium-taurocholate cotransporting polypeptide (NTCP, IC_{50}=19.6 μM or 12.3 μg/mL), bile salt export pump (IC_{50}=7.1 μM or 4.4 μg/mL), multidrug and toxin extrusion (MATE) protein 1 (IC_{50}=9.0 μM or 5.6 μg/mL), and MATE2K (IC_{50}=28.7 μM or 18.0 μg/mL) transporters. No or low inhibition (IC_{50} >50 μM or 31.3 μg/mL) of P-gp, multiple drug-resistance protein (MRP) 2, OAT3, organic cation transporter (OCT) 1, and OCT2 was observed.

Overall, from a perpetrator standpoint and based on the IC_{50} values and observed C_{max} values of 6.09 μM (3.8 μg/mL) in humans (at the highest BID dose of 200 mg proposed for Phase 2), JNJ-70033093 is not anticipated to cause clinically relevant DDIs with substrates of CYPs, UGT1A1, P-gp, NTCP, MRP2, MATE2K, OAT1, OAT3, OCT1, or OCT2 (IC_{50}=19.6 μM to >50 μM). However, there is a potential for DDIs with substrates of OATP1B1, OATP1B3, MATE1, or bile salt export pump at anticipated clinical doses and associated concentrations. In addition, a low potential for gastrointestinal interaction exists with substrates of P-gp and breast cancer resistance protein. From a victim standpoint, there is a potential for DDIs with inhibitors of CYP3A4/5 and P-gp, but not with inhibitors of OATPs.

Clinical Studies

JNJ-70033093 has been and is currently being investigated in a number of studies in humans, including:

- Single- and multiple-ascending dose study
- Drug-drug interaction study with itraconazole, diltiazem, rifampin, and aspirin
- Clinical pharmacology studies of special populations, including subjects with end-stage renal disease (ESRD) undergoing hemodialysis, renal impairment, and hepatic impairment
- Open-label safety and tolerability study in ESRD
- Relative bioavailability
- Japanese PK study
- Secondary stroke prevention study

To date, no dose-limiting safety findings have been observed in these studies.

Human Pharmacokinetics

The first-in-human study with JNJ-70033093 investigated single oral doses between 4 and 500 mg and multiple oral doses between 5 and 500 mg taken over a 14-day period. In the single-dose portion of the study, approximately dose proportional increases were observed between 20 and 200 mg once daily. Coadministration of a high-fat diet resulted in an approximately 1.4-fold increase in exposure at doses of 200 mg while 500 mg of JNJ-70033093 was associated with approximately 2-fold increases in exposure (AUC). Table 1 summarizes the clinical pharmacology of JNJ-70033093.

Table 1: Highlights of Clinical Pharmacology after Oral Administration of Single and Multiple Doses of JNJ-70033093 (BMS-986177) to Healthy Participants and Subjects with Renal or Hepatic Impairment

Properties	Clinical Results
T_{max}	2-4 hrs. Rapid absorption and quick onset PD effect
$T_{1/2}$	~11 hrs (terminal $T_{1/2}$); Suitable for BID or once daily dosing
Accumulation index	Accumulation ratio 1.14 – 1.75 for dose range 20-500 mg once daily, 3.99 for 200 mg BID in MAD
Exposure	Average C_{max}: 15.4 – 7,595 ng/mL; Average AUC: 172-95,110 ng x hr/mL
Proportionality	Greater than dose proportional from 4-20 mg and approximately dose proportional between 20-200 mg in SAD; Greater than dose proportional from 5-20 mg and dose proportional from 20-200 mg, and greater than dose proportional from 200-500 mg in MAD High-fat meal increases C_{max} by 53% and AUC by 39% at 200 mg, respectively and increases C_{max} by 80% and AUC by 110% at 500 mg, respectively
Metabolites	No significant metabolites
CYP3A4 inhibitors or inducer DDI	Itraconazole: 150% increase in AUC; 28% increase in C_{max} Diltiazem: 38% increase in AUC; 9% increase in C_{max} Rifampin: 85% decrease in AUC; 78% decrease in C_{max}
Aspirin DDI	Aspirin does not impact PK of JNJ-70033093; C_{max} and AUC of acetylsalicylic acid increased by 41% and 24%, compared to dosing of aspirin alone after 5 days
Japanese	Pharmacokinetics were comparable between Japanese participants and participants in CV010001 (mainly Caucasian)
Renal impairment[a]	C_{max} was similar for all renal function groups; AUC increased by 41% and 54% in participants with eGFR values of 30 and 15 mL/min/1.73 m^2, respectively, compared with a participant with normal renal function with an eGFR of 90 mL/min/1.73m^2 based on linear regression
Hepatic Impairment (normal hepatic impairment vs mild or moderate hepatic impairment)	Primarily metabolized in the liver - Similar C_{max} and AUC (0-INF) between normal, mild and moderate hepatic impairment groups Compared to normal participants - Mild hepatic impairment (Child Pugh A category): 18% ↑ in C_{max} and AUC(0-INF) - Moderate hepatic impairment (Child Pugh category B): 14% ↑ in C_{max} and no change in AUC(0-INF) When accounting for changes in protein binding, the differences in normal participants compared to: - Mild hepatic impairment (Child Pugh A category): 30% ↑ in C_{max} and 29% ↑ in AUC(0-INF) - Moderate hepatic impairment (Child Pugh category B): 41% ↑ in C_{max} and 24% ↑ in AUC(0-INF)
Relative bioavailability	Capsule formulation has similar PK profile to the SDD suspension used in Phase 1 studies

AUC=area under the plasma concentration-time curve; AUC(0-INF)=area under the plasma concentration-time curve (from zero to infinity); BID=twice daily; C_{max}=maximum observed concentration; CYP=cytochrome P450; DDI=drug-drug interaction; eGFR=estimated glomerular filtration rate; hr(s)=hour(s); MAD=multiple-ascending dose; PD=pharmacodynamics; PK=pharmacokinetic; SAD=single ascending dose; SDD: spray-dried dispersion; $T_{1/2}$=half-life; T_{max}=time to maximum concentration

a Preliminary results

Efficacy/Safety Studies

A recently completed multicenter, crossover, randomized, Phase 2a, proof-of-concept study in subjects undergoing hemodialysis for ESRD demonstrated that single doses of JNJ-70033093 up to 300 mg were safe and well tolerated and there were no reports of serious bleeding or other serious adverse events. An exploratory assessment of efficacy showed that the extent of clot

formation in the hemodialysis circuit for JNJ-70033093 was similar to the active comparators (unfractionated heparin and enoxaparin), suggesting that JNJ-70033093 has clinically meaningful antithrombotic activity at the doses tested (See IB, Edition 5).[21]

A recently completed DDI study showed that JNJ-70033093 200 mg BID, taken by healthy subjects over a 7-day period with aspirin, was safe and well tolerated, and the bleeding time did not increase significantly. Subjects enrolled into this study were allowed to take, if clinically indicated, low-dose aspirin (<100 mg once daily).[21]

Detailed information on Phase 1 and 2a studies in JNJ-70033093 is provided in the IB.[21]

2.2.1. Enoxaparin Sodium

The following information, taken from the European Union Summary of Product Characteristics (SmPC), is intended to provide a brief, representative overview of enoxaparin.

Enoxaparin sodium is a low molecular-weight heparin (LMWH), with a mean molecular-weight of approximately 4,500 daltons. In the in-vitro purified system, enoxaparin has a high anti-Factor Xa (anti-FXa) activity (approximately 100 IU/mg) and low anti-Factor IIa or antithrombin activity (approximately 28 IU/mg). These anticoagulant activities are mediated through antithrombin III, resulting in antithrombotic activities in humans. At the recommended doses, enoxaparin sodium does not influence bleeding time and global blood coagulation tests significantly, nor does it affect platelet aggregation or binding of fibrinogen to platelets.

Enoxaparin sodium is indicated in the European Union for the:

- Prophylaxis of thromboembolic disorders of venous origin, in particular those which may be associated with orthopedic or general surgery
- Prophylaxis of VTE in medical patients bedridden due to acute illnesses, including cardiac insufficiency, respiratory failure, or severe infections
- Treatment of venous thromboembolic disease presenting with deep vein thrombosis (DVT), pulmonary embolism (PE), or both
- Treatment of unstable angina and non-Q-wave myocardial infarction (MI), administered concurrently with aspirin
- Treatment of acute ST-segment elevation MI, including patients to be managed medically or with SC coronary intervention
- Prevention of thrombus formation in the extracorporeal circulation during hemodialysis

In patients with a higher risk of thromboembolism, such as orthopedic surgery, the recommended dosage of enoxaparin sodium given by SC injection is 40 mg (4,000 IU) once daily, with the initial dose administered preferably at least 12 hours preoperatively.

Enoxaparin treatment is prescribed as standard-of-care for an average period of 10 to 14 days or until the risk of thromboembolism has diminished. A longer treatment duration may be appropriate in some patients following hip replacement, and enoxaparin sodium may be

continued for as long as there is a risk of VTE and until the patient is ambulatory. Continued therapy with 40 mg once daily for 3 weeks following initial therapy has been proven to be beneficial in patients post-hip replacement.

For further information regarding enoxaparin refer to the SmPC or United States Prescribing Information. Although the 40-mg once daily dose of enoxaparin is not approved for TKR in the United States, it has been recently used as a comparator in a number of direct oral anticoagulant (DOAC) studies (eg, ADVANCE-2[28] and RECORD-3[24]).

2.3. Benefit/Risk Assessment

An estimated 920,000 patients in Japan and Europe experience VTE annually, which includes DVT and PE[6,22] and in the United States it is estimated that 900,000 patients experience a VTE annually, with 60,000 being fatal[5]. Joint replacement surgery of the lower extremities carries a high risk of VTE due to prothrombotic processes such as soft tissue and bone injury during surgery, which causes coagulation activation from thromboplastin release, venous stasis from peri- and postoperative immobilization, and inflammation from the healing process.[42] This has led to recommendations in the guidelines that all patients undergoing TKR surgery should receive pharmacologic and/or mechanical VTE prophylaxis.[12,22] Low molecular-weight heparin and several DOACs, including apixaban, rivaroxaban, dabigatran, and edoxaban have been used in the prevention of VTE in patients undergoing TKR surgery. However, limitations of these drugs include the possibility of an increased risk of bleeding at their recommended dosages. The concern of orthopedic surgeons about bleeding is a major obstacle to the use of anticoagulation in the perioperative period, even when clinical study data show that the absolute risk of bleeding is lower than the risk of VTE.[29]

As an inhibitor to the intrinsic coagulation pathway, JNJ-70033093 directly blocks the amplification process associated with the activation of the intrinsic pathway and the inherent risk of thrombosis associated with activation of this physiologic process. This can occur directly by contact activation of FXI or by thrombin-mediated feedback activation that would occur when the extrinsic pathway is activated. The extrinsic and common coagulation pathways are left intact, allowing for hemostasis to proceed. Therefore, in comparison with current standard-of-care, the use of JNJ-70033093, an inhibitor of a factor component of the intrinsic pathway, may have equal or greater efficacy with a reduced risk of bleeding.

Given that TKR surgery carries a high risk of VTE combined with the hemostatic challenges of surgery, it provides a good setting to evaluate the relative efficacy and safety (bleeding) characteristics of novel anticoagulants.[7] Patients who undergo elective total knee arthroplasty are at a high risk for the development of VTE with a 40% to 60% chance of developing asymptomatic DVT without any form of prophylaxis. It is estimated that 10% to 20% of distal DVT will extend into the proximal veins that carries with it a high risk of embolization and PE. In this setting, upwards of one-third of PEs will be fatal.[19] Therefore, TKR is an appropriate setting for testing new and potentially safer means of anticoagulation.

The available preclinical and clinical evidence suggest that direct inhibition of FXIa by JNJ-70033093 has the potential to reduce the risk of thromboembolic events with a lower risk of

major bleeding than currently available DOACs. While bleeding was not observed to any significant degree at the high doses of JNJ-70033093, either in healthy subjects or in those with ESRD undergoing hemodialysis, there is a potential risk of bleeding with any antithrombotic agent. Therefore, subjects will be closely monitored for bleeding, with oversight of the study by the Operations Committee (OC).

More detailed information about the known and expected benefits and risks of JNJ-70033093 may be found in the IB.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To determine the efficacy of JNJ-70033093 in preventing total VTE events (proximal and/or distal DVT [asymptomatic confirmed by venography assessment or objectively confirmed symptomatic], nonfatal PE, or any death) during the treatment period.	• Total VTE during the treatment period up to the time of venography as assessed by the CEC. Proof-of-efficacy is reached by either showing a positive dose-response or having less than a 30% total VTE event rate in the combined BID dose group.
Secondary	
• To assess the dose-response of JNJ-70033093 for the occurrence of the endpoint of any bleeding events during the treatment period.	• The composite endpoint of any bleeding event on treatment. Any bleeding will be defined as the composite of major bleeding according to the ISTH criteria modified for the surgical setting, clinically relevant nonmajor bleeding events, or minimal bleeding events as assessed by the CEC.
• To determine the efficacy of JNJ-70033093 in preventing total VTE events during the full study period.	• Total VTE as assessed by the CEC through Week 6.
• To assess the dose-response of JNJ-70033093 for the rate of any bleeding throughout the full study period.	• Occurrence of the composite endpoint of any bleeding events, the composite endpoint of major or clinically relevant nonmajor bleeding events, and the individual components of the composite endpoint of any bleeding as assessed by the CEC through Week 6.
• To assess the dose-response of JNJ-70033093 for the prevention of major VTE (death, asymptomatic or symptomatic proximal DVT or PE) during the treatment period and throughout the full study period.	• Major VTE as assessed by the CEC during the treatment period and through Week 6.
• To assess the effect of individual doses of JNJ-70033093 compared with enoxaparin for both efficacy and safety endpoints.	• Total VTE and any bleeding as assessed by the CEC during the treatment period and during the full study period (6 weeks).
• To compare the effect of JNJ-70033093 with enoxaparin for the individual components of the total VTE endpoint.	• All individual components of the primary efficacy endpoint as assessed by the CEC during the treatment period and during the full

Objectives	Endpoints
	study period (6 weeks).
• To assess the PK of JNJ-70033093 in men and women undergoing primary unilateral TKR surgery and the relation of these measures to efficacy and safety endpoints (eg, exposure-response analyses).	• Estimation of PK parameters and the effects of demographics and laboratory values (eg, body weight, age, gender, renal function) on the PK of JNJ-70033093. • Estimation of the relationship between JNJ-70033093 exposure with probability of total VTE during the treatment period up to the time of venography and the probability of the composite endpoint of major or clinically relevant nonmajor bleeding events, and the individual components of the composite endpoint of any bleeding event on treatment.
Exploratory	
• To evaluate PD to assess its relationships to PK and the relation of these measures to efficacy and safety endpoints (eg, exposure-response analyses).	• Changes in PD (aPTT, PT, FXI clotting activity, anti-FXa activity, and TGA). • Estimation of the relationship between JNJ-70033093 exposure with the changes in PD.
• To evaluate exploratory biomarkers to assess their relationship to the probability of total VTE during the treatment period.	• Estimation of the changes in biomarkers with the probability of total VTE during the treatment period up to the time of venography and the probability of the composite endpoint of major or clinically relevant nonmajor bleeding events, and the individual components of the composite endpoint of any bleeding event on treatment.
• Explore the presence and incidence of asymptomatic MINS as it relates to total knee arthroplasty.	• The presence of an isolated elevated hs-cTnT measurement postoperatively without an alternative explanation (eg, sepsis, atrial fibrillation) in subjects with normal preoperative hs-cTnT. An incremental rise in hs-cTnT without an alternate explanation in individuals with elevated preoperative hs-cTnT.

anti-FXa=anti-Factor Xa; aPTT=activated partial thromboplastin time; CEC=Clinical Endpoint Committee; DVT=deep venous thrombosis; FXI=Factor XI; hs-cTnT=high-sensitive cardiac troponin T; ISTH=International Society on Thrombosis and Hemostasis; MINS=myocardial injury in noncardiac surgery; PD=pharmacodynamic; PE=pulmonary embolism; PK=pharmacokinetic; PT=prothrombin time; TGA=thrombin generation assay; TKR=total knee replacement; VTE=venous thromboembolism

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

The primary hypothesis is that JNJ-70033093 reduces the risk of total VTE during the treatment period. This can be achieved by either a statistically significant dose-response trend or an event

rate for the combined BID doses of JNJ-70033093 that is statistically lower than 30%. The event rate of 30% is a conservative estimate of the total VTE rate in subjects given placebo.

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, study drug-dose blind, active-controlled, multicenter, dose-ranging study of JNJ-70033093 in subjects undergoing primary unilateral elective TKR surgery. The study uses the prospective, randomized, open-label, blinded endpoint (PROBE) design. Men and women who are ≥50 years of age are eligible to participate if they are considered medically stable and appropriate for anticoagulant prophylaxis as determined by the investigator and on the basis of clinical laboratory tests performed as part of screening for elective TKR surgery. A target of 900 subjects will be randomly assigned to treatment in this study, with an option to increase the randomization target to approximately 1,200 subjects based on the possible addition of once daily dose groups, and/or evaluability rate.

Subjects meeting all of the enrollment criteria will be eligible to enter the study. The study will be conducted in 3 phases, which includes an up to 30-day screening phase before surgery, a 10- to 14-day postoperative dosing phase, and a 4-week ±10 days follow-up phase. Unscheduled visits may be performed at the discretion of the investigator for the assessment of any potential bleeding or efficacy endpoint events. The total duration of participation following randomization will be approximately 6 weeks.

Screening for eligible subjects will be performed within and including 30 days before administration of the first dose of postoperative study drug. Eligible subjects will be randomly assigned to treatment with either JNJ-70033093 or enoxaparin postoperatively following unilateral elective TKR surgery. Subjects will know the treatment to which they were assigned but subjects randomly assigned to JNJ-70033093 will remain blinded to the dose and frequency (ie, BID versus once daily).

First dosing of both study drugs will occur while the subject is still hospitalized, with administration beginning a minimum of 12 hours and a maximum of 24 hours after the end of TKR surgery, which is defined as the time of wound closure, and must be the first anticoagulant administered postoperatively.

Enoxaparin may be administered preoperatively 12 hours prior to the surgical procedure in accordance with local standard-of-care. Sites that routinely administer preoperative enoxaparin should continue their standard practice for all study subjects at that site. Per standard-of-care, study drug should not be used for the preoperative dose of enoxaparin for subjects in either treatment group.

Following discharge or transfer to an alternate facility, subjects will continue to take the assigned study drug for a total of 10 to 14 days as described in Section 6.1, Study Drugs Administered. Unilateral venography assessment of the operated leg will be performed within 1 calendar day after the last dose of either JNJ-70033093 or enoxaparin is taken.

Subjects will return to the study-site 6 weeks after the TKR surgery for study-related evaluations and procedures as described in the Schedule of Activities. Safety evaluations will include the monitoring of all adverse events, including nonserious adverse events, serious adverse events, adverse events of interest (ie, bleeding events, liver enzyme elevations and clinical liver events, wound or joint complications), clinical laboratory tests (ie, hematology, clinical chemistry, urinalysis), and physical examinations.

Selected sites may also use scanning technology to manage clinical study supplies and drug compliance activities. Subject's enrolled at selected sites may use an application on the subject's own smartphone/tablet to confirm study drug administration (JNJ-70033093 capsules only) and receive notifications as per protocol scheduled events (eg, next clinical site visit) as well as additional study information.

An OC, Steering Committee, and independent Clinical Events Committee (CEC) will be commissioned for this study. The OC will be unblinded and the Steering Committee will be blinded to the dose and frequency of JNJ-70033093, unless the OC finds it necessary to consult with and unblind select members of the Steering Committee. If any members of the Steering Committee are unblinded, they will no longer be involved in the operational conduct of the study. The CEC will be blinded to both the study drug and the dose. The OC will be responsible for reviewing ongoing safety and efficacy data by unblinded subject treatment assignments approximately every 3 to 8 weeks on a periodic basis. Refer to Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations for details.

Unblinded periodic and interim analyses will be conducted by the OC for the purposes of safety oversight and as part of the adaptive approach. The first interim analysis will be triggered when approximately 300 subjects (approximately 50 subjects in each of the JNJ-70033093 BID treatment groups) have completed venography or have had a symptomatic VTE event. Both periodic and the interim analyses results will be used to guide the decision to drop a dose of JNJ-70033093 and/or readjust the randomization ratio. The number of subjects who were planned to be randomized into the dropped dosing regimen can be allocated to one of the other dosing groups. The interim analysis will also serve as the formal venue to assess study status and possibly add once daily dosing of JNJ-70033093 based on available efficacy and safety data. If PK/PD analysis results are available at the time of the interim analysis, the results will be included in the review.

Additional interim analyses will be conducted, as needed, at the discretion of the OC.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Intervention Groups

Randomization will be used to minimize bias in the assignment of subjects to study drug and dose groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across study drug groups, and

to enhance the validity of statistical comparisons across study drug groups. Subjects will be unblinded as to the study drug assignment (JNJ-70033093 or enoxaparin); however, they will remain blinded to the dose and frequency and the adjudication of clinical endpoint events will be conducted in a blinded fashion by an independent CEC to reduce potential bias during the evaluation of clinical endpoints.

Study Population

Total knee replacement is most commonly performed in older men and women to correct arthritic disease of the joint. Given that the risks of VTE and bleeding increase with age, the study has been appropriately designed to include both men and women who are at least 50 years of age. The risk of VTE following major orthopedic surgery, specifically joint replacement surgery, has been well documented, and the use of postoperative prophylactic anticoagulant therapy is widely accepted as standard-of-care.[12,22] Over the past 20 years, Phase 2 studies of injectable anticoagulants (LMWH, fondaparinux) and newer oral anticoagulants (apixaban, rivaroxaban, dabigatran, and edoxaban) were conducted in this population using venography to detect asymptomatic DVT.[11,17,20,27,28,39]

Choice of Comparator

This study will use LMWH as the comparator for consistency with all of these health-authority approved oral medications that were evaluated in large, similarly designed Phase 3 studies for the prevention of VTE in TKR surgery and also because it continues to be used widely for prophylaxis. Given that VTE and bleeding event rates vary across studies, the active control will also provide an internal reference for comparison with JNJ-70033093 in this study.

As one of the most widely used anticoagulants in joint arthroplasty, enoxaparin has been used as a comparator for the currently approved DOACs.[41] Consistent with this approach, enoxaparin was chosen as the comparator in this study. Enoxaparin is approved worldwide for this indication and has demonstrated favorable efficacy and safety (ie, bleeding) results. Refer to Section 2.2.1, Enoxaparin sodium for additional details.

The 40-mg daily dose of enoxaparin will be used in this study as it is the dosage regimen used in most approved countries for the indication being studied. Enoxaparin will be administered once daily for 10 to 14 days, with an option to begin the first dose at least 12 hours before surgery, which is preferred by some surgeons, or 12 to 24 hours after the end of TKR surgery, defined as the time of wound closure.

Choice of Efficacy Measures

Total VTE is a standard efficacy measure for Phase 2 TKR VTE prophylaxis studies. The use of venography to detect asymptomatic DVT and standardized definitions to assess symptomatic venous thromboembolism are specifically recommended as the best approach for the Phase 2 orthopedic surgery setting.[7] The assessment time between Days 10-14 is appropriate given that it is a usual period of anticoagulation following TKR surgery as well as other forms of anticoagulation (eg, DOACs).

Ultrasound is a noninvasive, widely available technique, with a high sensitivity and specificity for symptomatic DVT that has replaced venography in clinical practice for the diagnosis of DVT events (all DVT sensitivity 88%, specificity 96%).[23] However, ultrasound has repeatedly been shown to have very low sensitivity compared with venography for detecting asymptomatic DVT in the postoperative setting.[23,34] In a meta-analysis of 15 studies, the sensitivity of ultrasound compared with venography for detecting asymptomatic DVT was 47%.[23] More recent data are from the Phase 2 studies of rivaroxaban in DVT prophylaxis following hip and knee replacement surgeries, where a substudy (VENUS study) was conducted comparing venography to ultrasound. Despite rigorous methodology, including separate adjudication sites for each technique and a large number of matching pairs of evaluable venography assessments and ultrasounds, the authors concluded that ultrasound cannot replace venography for DVT diagnosis in this setting. The observed frequency of any DVT was 18.9% with venography and 11.5% with ultrasound. The sensitivity of ultrasound compared with venography was 31.1% (95% CI: 23.4, 38.9) for any DVT, 21.0% (95% CI: 2.7, 39.4) for proximal DVT, and 30.8% (95% CI: 23.1, 38.6) for distal DVT. The results for specificity were 93.0% (95% CI: 91.0, 95.1), 98.7% (95% CI: 98.0, 99.5), and 93.3% (95% CI: 91.5, 95.3), respectively.[34]

Therefore, venography is still considered the gold standard and the only reliable method for diagnosing asymptomatic DVT after TKR surgery. The most likely explanations for the poor performance of ultrasound compared with venography in this setting are the nature of the clots that form early after surgery (small and compressible) compared with symptomatic clots (larger and noncompressible) and the distortion of the veins produced by postoperative swelling.

Although research into new anticoagulants has slowed in recent years, all proof-of-concept studies using the postoperative orthopedic model have continued to use venography to assess the primary endpoint.[4,14,26,40] Venography produces plausible and reliable results in clinical studies[7,19,36] and no anticoagulant has been approved by a health-authority for postoperative orthopedic DVT prophylaxis without venography data. Despite the challenges with performing venography, it remains the standard for detecting DVT after TKR surgery and is the most appropriate method for use in this study.

Bilateral venography has been used in most but not all previous Phase 3 studies.[15,17] Venography of the operated leg will be performed in this study. Unilateral venography of the operated leg detects over 90% of DVTs after TKR surgery[16] and exposes subjects to less risk (radiation, contrast dye, venipuncture) and less discomfort.

Choice of Safety Measures/Assessments

Bleeding events are the standard primary safety endpoint in studies of anticoagulant VTE prophylaxis after TKR surgery. Because the occurrence of major bleeding events is infrequent and previous dose-ranging studies have demonstrated that all categories of bleeding events increase with dose in a similar manner, the any bleeding event composite will be the primary safety endpoint in this study.[25] Published guidelines that describe how to define major bleeding events after major orthopedic surgery will be followed.[35] For nonmajor bleeding events, standardized definitions, as utilized in the Phase 3 TKR studies of apixaban, will be

followed.[27,28] All wound or joint complications will also be specifically assessed in this study as these are important from the perspective of both the subject and the surgeon.

Choice of PK Measures

Pharmacokinetic blood samples will be collected and analyzed for subjects who are randomly assigned to treatment with JNJ-70033093 to further understand the PK characteristics and variability and assess the exposure-response of JNJ-70033093 in the TKR patient population.

Choice of PD Measures

Samples will be collected to evaluate the PD effect on the target of JNJ-70033093 or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to an intervention. The goal is to evaluate the PD of JNJ-70033093 and aid in evaluating the intervention-clinical response relationship.

Choice of Biomarkers

Myocardial injury after noncardiac surgery is the most frequent vascular complication to occur perioperatively with an estimated frequency of approximately 8%. Affecting about 8 million adults worldwide, patients experiencing myocardial injury in noncardiac surgery (MINS) are at increased risk of death or cardiovascular complication. It is estimated that 85% of MINS occurs within 48 hours of surgery.[8] Unlike the traditional definition of MI, MINS does not require symptoms or evidence of ischemia (eg, ST changes). In the VISIONS study, only 16% of subjects experiencing MINS had symptoms of an ischemic feature.[2] In an observational study involving a tertiary care center, Rubin and colleagues estimated that the incidence of MINS in orthopedic procedures is approximately 19%.[33]

In this study, subjects will have cardiac troponins drawn postoperatively on Day 1 (0 hour) prior to study drug administration and Day 10-14; data derived from these analyses will be used to estimate the presence of MINS.

Factor XI antigen will also be used as a biomarker for potential bleeding and as an efficacy signal. Recent studies suggest that high levels of FXI are associated with increased risk for venous thrombosis and stroke, whereas reduced FXI levels are associated with protection from VTE. In addition to activation by Factor XIIa, FXI can also be activated by thrombin in a positive feedback reaction, further propagating thrombus growth. Measurement of FXI antigen in plasma at baseline, using a validated immunoassay, may help to improve understanding of thrombotic conditions and help identify subjects susceptible to cardiovascular events.[13,31,44]

4.2.1. Study-Specific Ethical Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

JNJ-70033093 is an investigational drug that is being developed for multiple thrombosis-mediated conditions. The nonclinical and clinical data obtained to date with JNJ-70033093 support administration of multiple doses in a well-controlled clinical research study. The present study is needed to support further clinical development of JNJ-70033093, and the study design is based on sound scientific rationale, as described in this protocol. Thorough scientific evaluation of any promising treatment before marketing authorization is an ethical requirement. In the continuing search for medications with improved efficacy and safety profiles, it is necessary to fully investigate and understand new products.

The primary ethical concern is that the safety and efficacy profile of JNJ-70033093 has not been fully established as it has only been studied in a limited number of subjects. Subjects in this study who are at risk for VTE following TKR surgery are being asked to take a new treatment for the prevention of VTE. Based on the nonclinical and Phase 1 clinical studies, a range of doses of JNJ-70033093 has been selected for further evaluation in this study. Preclinical studies looking at clot formation demonstrated that doses equivalent to 25 mg BID reduced clot formation by 50%.

The primary risk with any anticoagulant drug is the potential for bleeding events. Based on the nonclinical evaluations of JNJ-70033093, the risk for these events is anticipated to be low (ie, all planned doses are below those shown to have a statistically significant increase in bleeding risk). No bleeding signal was detected at the 200-mg BID dose in healthy male subjects. Subjects in this study will be carefully observed for bleeding events throughout the duration of the study and management strategies for each type of event are outlined in the protocol (see Section 8.2.1.2, Approach to Subjects With a Bleeding Event).

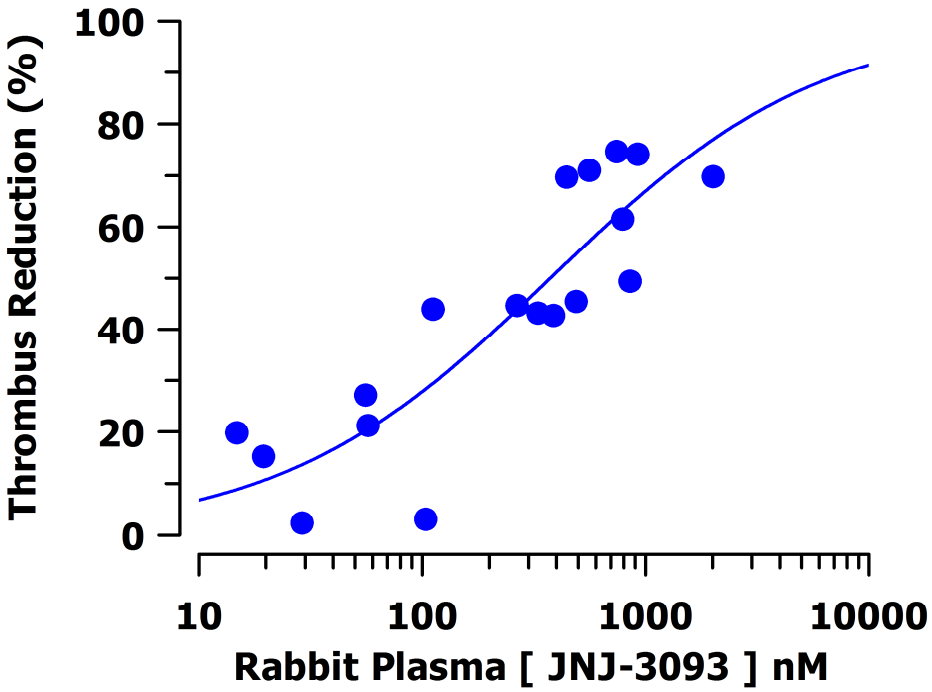
Venography assessments will be used to evaluate for the presence of DVT. The x-ray used in the imaging exposes the body to a small dose of ionizing radiation. The risks of radiation exposure may be tied to the number of x-rays and x-ray treatments a person has had over their lifetime. Given that all subjects in this study will be ≥50 years of age, the incremental risk of this radiation exposure is considered small. X-rays are the oldest and most frequently used form of medical imaging. Other risks associated with venography assessments include pain, infection, and/or bleeding at the site of venous access and the risks from contrast medium administration (ie, allergy, nephrotoxicity, and/or possible irritation of the venous system leading to the development of DVT). In previous studies, venography assessments have been well tolerated and do provide clinically useful information about the presence or absence of DVT following surgery.[32,38]

There may be risks associated with venipuncture and multiple blood sample collection, including prolonged bleeding due to the anticoagulant effects of JNJ-70033093. The total blood volume to be collected for safety, PK, PD, and biomarker laboratory tests is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the World Health Organization (WHO) for standard blood donation volume for healthy donors (standard donation of 350 [body weight >45 kg] to 450 [body weight >50 kg] mL every 12 weeks [males] to 16 weeks [females]).[43]

4.3. Justification for Dose

Identification of effective doses of JNJ-70033093 was based on inhibition of thrombus formation in a rabbit model of electrically induced carotid artery thrombus (ECAT) in rabbits. The rabbit ECAT model has been calibrated against clinical results in VTE prevention based on apixaban. In this model, targeting the concentration that led to 50% reduction in thrombus weight was correlated with the steady-state trough concentration of the clinical dose of apixaban. In the rabbit ECAT model, JNJ-70033093 caused a dose-dependent decrease in both clot weight (Figure 2) and preservation of blood flow without a significant increase in bleeding time. The equivalent to half the maximal effective concentration (EC_{50}) plasma concentrations in the rabbit ECAT model was 235 ng/mL (375 nM). Making corrections for the difference in potency in human versus rabbit FXIa (where JNJ-70033093 is more potent than rabbit FXIa) and the differences in plasma protein binding between human versus rabbit (where protein binding is lower in human versus rabbit plasma) yields a human target of 34.5 ng/mL (55 nM) as the trough target concentration.[21]

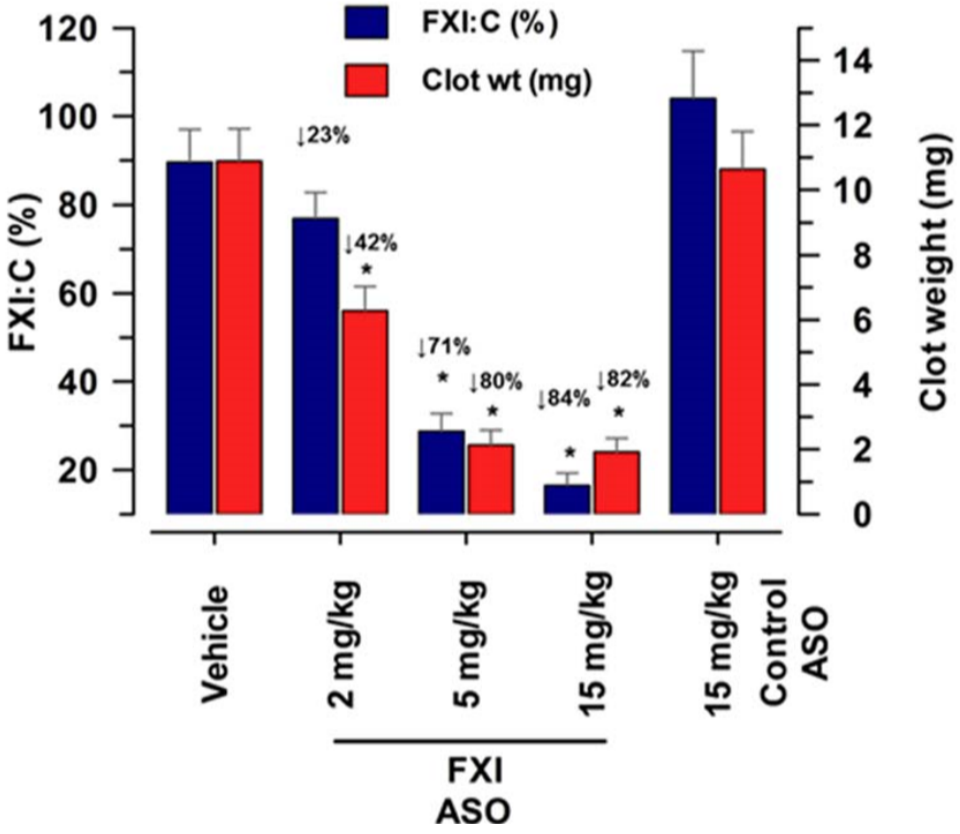
Figure 2: Exposure-dependent Reductions in Thrombus Weights With JNJ-70033093 in Rabbits



A Phase 2 study for VTE prophylaxis post TKR provides the only published data on the clinical safety and efficacy of reducing FXI activity. Subjects were treated for 36 days prior to surgery with an ASO to reduce the level of FXI. The study showed a dose-dependent reduction in the risk of VTE events compared with enoxaparin. Doses that did not reduce FXI levels to 20% or less of normal did not reduce the risk of VTE events compared with enoxaparin.[4] About a 1.5-fold prolongation in aPTT was observed at the dose that reduced FXI levels to 20% or less of normal. Figure 3 shows the dose-dependent decrease in FXI levels and clot weight observed in

the rabbit ECAT model with ASO-induced inhibition of FXI.[21] Based on the dose-dependent reduction of FXI concentrations observed in the ASO VTE prevention study (ISIS 416158), a trough concentration of approximately 150 ng/mL of JNJ-70033093 was necessary to achieve an antithrombotic effect equal to the 80% reduction in FXI level in the rabbit ECAT model.

Figure 3: Reduction in FXI Concentration Based on FXI ASO Compound Used in Phase 2 VTE Study



ASO=antisense oligonucleotide; C=concentration; FXI=Factor XI; FXI ASO=Factor XI antisense oligonucleotide; VTE=venous thromboembolism

Based on data obtained from healthy subjects, population PK modeling indicates that doses likely to achieve the trough concentration targets based on apixaban and ASO for a VTE prevention study are between 100 to 200 mg once daily and 25 to 50 mg BID. A 50-mg once daily dose prolongs the aPTT 1.5-fold for about 24 hours in healthy volunteers and the plasma concentrations achieved are above those required for antithrombotic efficacy (EC50) in the rabbit ECAT model of thrombosis for a sustained period time. The data indicating coverage of the target concentrations in the rabbit ECAT model for both apixaban and the FXI inhibitor ASO, supports the potential for JNJ-70033093 to provide similar or greater efficacy in patients. Finally, a lower risk of bleeding is anticipated with inhibition of FXIa than with inhibition of Factor Xa (FXa), based on the mechanistic rationale for targeting the intrinsic pathway via inhibition of FXIa.

4.4. End of Study Definition

A subject will be considered to have completed the study if he or she has completed assessments at Week 6 or has died prior to Week 6.

Subjects who prematurely discontinue the study drug for any reason before completion of the postoperative dosing phase can be considered to have completed the study if they have completed follow-up at Week 6.

The end of the study is considered the last visit for the last subject in the study. The final data from the study-site will be sent to the sponsor (or designee) after completion of the final subject visit at that study-site, in the time frame specified in the Clinical Trial Agreement.

5. STUDY POPULATION

Screening for eligible subjects will be performed within and including 30 days before administration of the first dose of postoperative study drug. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling subjects in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 9.1, Sample Size Determination.

5.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Male or female.

2. 50 years of age, or older.

3. Medically stable and appropriate for anticoagulant prophylaxis as determined by the investigator on the basis of physical examination, medical history, and vital signs performed as part of screening for elective TKR surgery.

4. Medically stable and appropriate for anticoagulant prophylaxis on the basis of clinical laboratory tests performed as part of local standard-of-care as part of screening for elective TKR surgery. If the results of laboratory tests are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the investigator.

5. Has plans to undergo an elective primary unilateral TKR surgery.

6. Must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects in clinical studies.

7. A woman of childbearing potential (WOCBP) must have a negative urine or highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) up to 2 days before the administration of the study drug.

8. Criterion modified per Amendment 1

   8.1. A woman must be (as defined in Section 10.5, Appendix 5, Contraceptive and Barrier Guidance and Collection of Pregnancy Information).

   a. Not of childbearing potential
   b. Of childbearing potential and
      - Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method for the duration of study drug with JNJ-70033093 plus 5 half-lives of study drug plus 30 days (duration of ovulatory cycle) for a total of 34 days after the completion of treatment. Examples of highly effective methods of contraception are located in Section 10.5, Appendix 5, Contraceptive and Barrier Guidance and Collection of Pregnancy Information.
      - Pregnancy testing (serum or urine) prior to the first dose of study drug.

9. Criterion modified per Amendment 1

   9.1. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 34 days after the last dose.

10. Criterion modified per Amendment 1

    10.1. A male subject must wear a condom when engaging in any activity with a WOCBP during the study and for the duration of treatment with JNJ-70033093 plus 5 half-lives of the study drug plus 90 day (duration of sperm turnover) for a total of 94 days after the completion of treatment. Male subjects should also be advised of the benefit for a female partner to use a highly effective method of contraception as a

condom may break or leak. This criterion does not apply to male subjects randomly assigned to enoxaparin.

11. Criterion modified per Amendment 1

    11.1. A male subject must agree not to donate sperm for the purpose of reproduction during the study and for the duration of treatment with JNJ-70033093 plus 5 half-lives of the study drug plus 90 days (duration of sperm turnover) for a total of 94 days after the completion of treatment. This criterion does not apply to male subjects randomly assigned to enoxaparin.

12. Willing and able to adhere to the lifestyle restrictions (Section 5.3, Lifestyle Considerations) specified in this protocol.

5.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. History of any condition for which the use of LMWH is not recommended in the opinion of the investigator (eg, previous allergic reaction, creatinine clearance <30 mL/minute).

2. History of severe hepatic impairment.

3. Planned bilateral revision or unicompartmental procedure.

4. Criterion modified per Amendment 1

   4.1. Planned postoperative epidural analgesia with an epidural catheter.

   - If an epidural catheter was used, it must be removed at least 5 hours prior to postoperative study drug administration.

   NOTE: if a subject had an epidural or spinal anesthesia procedure with bleeding or significant trauma at the time of surgery, they should not be randomized.

5. Criterion modified per Amendment 1

   5.1. Unable to undergo venography (eg, due to contrast agent allergy, poor venous access, or impaired renal function that would increase the risk of contrast-induced nephropathy).

6. Known previous PE or DVT in either lower extremity.

7. Known allergies, hypersensitivity, or intolerance to JNJ-70033093 or its excipients (refer to IB).

8. Criterion modified per Amendment 1

   8.1. Contraindications to the use of or known allergies, hypersensitivities, or intolerance to enoxaparin per local prescribing information (eg, heparin and pork products).

9. Any condition requiring chronic antithrombotic therapy (eg, atrial fibrillation, mechanical heart valve, recent coronary intervention), except for aspirin ≤100 mg per day.

10. Use of strong CYP3A4/P-gp inhibitors or strong CYP3A4/P-gp inducers in the 7 days prior to randomization or the need for ongoing treatment with concomitant oral or IV therapy with strong CYP3A4/P-gp inhibitors or strong CYP3A4/P-gp inducers during the treatment period.

11. Taken any disallowed therapies as noted in Section 6.5, Concomitant Therapy before the planned first dose of study drug.

12. Planned use of intermittent pneumatic compression after the first postoperative dose of the study drug.

13. Received an investigational study drug (including investigational vaccines) or used an invasive investigational medical device within 60 days before the planned first dose of study drug or is currently enrolled in an investigational study.

14. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

15. Has surgery planned (except the TKR study) during the time the subject is expected to participate in the study for which anticoagulant therapy would be interrupted.

16. Previously randomized subject in this study or participated in previous studies with JNJ-70033093.

17. Employee of the investigator or study-site, with direct involvement in the proposed study or other studies under the direction of that investigator or study-site, as well as family members of the employees or the investigator.

18. At the time of informed consent, the subject does not agree to following up with scheduled study visits or allowing a telephone contact to the subject's alternative means of contact (eg subject's children, spouse, significant other, caretaker, legal representative, healthcare professional), as necessary, until the end of the study, should he or she discontinue prematurely.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before randomization such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for rescreening. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations. Randomized subjects must also meet these criteria prior to the first dose of the study drug.

5.3. Lifestyle Considerations

Potential subjects must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.5, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

3. Criterion modified per Amendment 1

   3.1. Avoid donating blood until after completion (ie, final follow-up visit) of the study.

4. Criterion modified per Amendment 1

   4.1. A WOCBP must agree to use one of the contraceptive methods allowed during the study for a minimum of 34 days after receiving the last dose of study drug as described in Section 10.5 of Appendix 5, Contraceptive and Barrier Guidance and Collection of Pregnancy Information. All men who are randomly assigned to JNJ-70033093 and are sexually active with a WOCBP must agree to use a condom and must also not donate sperm for a minimum 94 days after receiving the last dose of study drug.

5.4. Screen Failures

Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports will identify subjects by subject identification number and age at initial informed consent.

In cases where the subject is not randomized into the study, the date seen and age at initial informed consent will be used.

Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Subjects may only be rescreened on 1 occasion.

6. STUDY TREATMENT

6.1. Study Drugs Administered

Drug Administration

JNJ-70033093 will be provided as capsules for oral administration. Subjects will be instructed to take their assigned dose of the study drug orally each day. The study drug is to be taken with approximately 240 mL (8 ounces) of water. The capsules should be swallowed intact and subjects should not attempt to dissolve them in water. Each dose should be taken at approximately the same time each day. If a dose is missed, the capsules should be taken as soon as possible; 2 doses can also be taken together in the evening if the morning dose is missed. If an evening dose is missed it should not be taken with the next morning dose; no more than 2 doses (4 capsules) should be taken in 1 day.

Eligible subjects will be randomly assigned to treatment with either JNJ-70033093 or enoxaparin postoperatively following unilateral elective TKR surgery. Subjects will know the treatment to which they were assigned but subjects randomly assigned to JNJ-70033093 will remain blinded to the dose and frequency (ie, BID versus once daily).

First dosing of both study drugs will occur while the subject is still hospitalized, with administration beginning a minimum of 12 hours and a maximum of 24 hours after the end of TKR surgery, which is defined as the time of wound closure, and must be the first anticoagulant administered postoperatively.

Enoxaparin may be administered preoperatively 12 hours prior to the surgical procedure in accordance with local standard-of-care. Sites that routinely administer preoperative enoxaparin should continue their standard practice for all study subjects at that site. Per standard-of-care, study drug should not be used for the preoperative dose of enoxaparin for subjects in either treatment group.

Study visits should be conducted in the morning, when possible and study drug dosing on the day of a study visit should not occur until after the PK sample has been drawn. On the day of the Day 10-14 visit, study drug dosing should occur first thing in the morning, and the PK sample should not be drawn until at least 1 hour after the dose is taken.

At the time of the interim analysis, the OC may implement a once daily dosing regimen(s) of 50 and/or 200 mg of JNJ-70033093. Postoperative administration of the study drug will occur after the TKR surgery, while the subject is still hospitalized and with a minimum of 12 hours and a

maximum of 24 hours after the end of TKR surgery, defined as the time of wound closure, and must be the first anticoagulant administered postoperatively. On Day 1 and Day 4, the 12-hour PK samples should be drawn before administering the next scheduled dose of study drug. If using the +6-hour window to allow the 12-hour sample to be drawn the following morning, the evening dose of study drug on Day 1 or Day 4 should be administered, but there must be a minimum of 6 hours between doses on these days.

Study drug administration must be captured in the source documents and the electronic case report form (eCRF). Study-site personnel will instruct subjects on how to store study drugs for at-home use as indicated for this protocol.

Dosing

This study has an adaptive design, with the intent to optimize data collection for the dose-response evaluation using multiple comparison procedures and modeling (MCP-Mod). Initially, eligible subjects will be randomly assigned in a 1:1:1:1:2 ratio to 1 of 5 parallel treatment groups, including 4 dose regimens of JNJ-70033093 or enoxaparin 40 mg once daily given subcutaneously for 10 to 14 days.

The number of dose regimens, the option to implement once daily dosing regimens, and the randomization ratio will depend on the unblinded analysis results and the review by the OC.

JNJ-70033093

Each subject randomly assigned to JNJ-70033093 will take 4 capsules a day, 2 capsules in the morning and 2 capsules in the evening at approximately the same time each day, as follows:

- Group A: JNJ-70033093 25 mg BID (1 capsule JNJ-70033093 25 mg and 1 placebo capsule, BID)
- Group B: JNJ-70033093 50 mg BID (2 capsules JNJ-70033093 25 mg BID)
- Group C: JNJ-70033093 100 mg BID (1 capsule JNJ-70033093 100 mg and 1 placebo capsule, BID)
- Group D: JNJ-70033093 200 mg BID (2 capsules JNJ-70033093 100 mg BID)
- Group E: JNJ-70033093 25 mg once daily (1 capsule JNJ-70033093 25 mg and 1 placebo capsule in the morning and 2 placebo capsules in the evening). Enrollment in this group discontinued per Amendment 1. Subjects randomized to this group prior to Amendment 1 will complete study drug treatment and study procedures
- Group F: JNJ-70033093 200 mg once daily (2 capsules JNJ-70033093 100 mg in the morning and 2 placebo capsules in the evening). Enrollment in Group F suspended per Amendment 1 and will become optional depending on the OC decision. Subjects randomized to this group prior to Amendment 1 will complete the study drug treatment and study procedures
- Group G: JNJ-70033093 50 mg once daily (2 capsules JNJ-70033093 25 mg in the morning and 2 placebo capsules in the evening). Enrollment in Group G will become optional depending on the OC decision per Amendment 1

Subjects randomly assigned to JNJ-70033093 who take the first dose of study drug on the evening of surgery should take the 2 capsules assigned to the Day 1 morning dose (left side of blister card). On subsequent days, the first dose should always be the left 2 capsules and the evening dose should be the 2 capsules on the right.

JNJ-70033093 will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

Enoxaparin

Subjects randomly assigned to enoxaparin (Group I) will receive a SC dose of enoxaparin 40 mg once daily, supplied as a prefilled syringe.

6.2. Preparation/Handling/Storage/Accountability

All oral study drug must be stored at controlled temperatures ranging as specified on the product label. Enoxaparin will be stored in accordance with the approved product labeling which is also specified on the product label.

Refer to the pharmacy manual/study-site investigational product and procedures manual for additional guidance on study intervention preparation, handling, and storage.

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Selected sites may use scanning technology to manage clinical study supplies (JNJ-70033093 and enoxaparin) and drug compliance activities (JNJ-70033093 only).

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study-site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the drug return form. When the study-site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner in a disposal container. The disposal container will be retained for verification purposes.

Study drug should be dispensed under the supervision of the investigator or an appropriate delegate and qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must

not be dispensed again, even to the same subject. Whenever a subject brings his or her study drug to the study-site for pill count, this is not considered a return of supplies. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Dynamic central randomization will be implemented in conducting this study. Initially, subjects will be assigned to 1 of 5 study drug groups based on an algorithm implemented in the interactive web response system (IWRS) before the study. Following the interim analysis, the IWRS will be updated for randomization accordingly. Subjects will be stratified by region using dynamic central randomization to minimize the imbalance in the distribution of the number of subjects across study drug groups. Based on the algorithm, the IWRS will assign a unique study drug code, which will dictate the study drug assignment and matching study drug kit for the subject.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the dosing blind for an individual subject.

Subjects will be unblinded as to their treatment assignment but those subjects randomly assigned to JNJ-70033093 will be blinded to the dose and regimen (ie, BID versus once daily). Under normal circumstances, the JNJ-70033093 dosing regimen blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the dose of the treatment by contacting the IWRS. While the responsibility to break the blind in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and time for the unblinding must be documented by the IWRS and reason for the unblinding must be documented in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects randomized to JNJ-70033093 who have had their treatment dose assignment unblinded may continue on study drug unless the subject meets a study drug discontinuation criterion as described in Section 7.1, Discontinuation of Study Drug. Investigators should not disclose the treatment dose assignment to the subject whenever possible, even in a special situation where the

treatment dose assignment has been unblinded to the investigator. Subjects who have had their treatment dose assignment unblinded should continue to return for scheduled evaluations.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized individuals of the OC for the periodic data reviews and interim analyses, it will only be for those subjects included in the analysis. Refer to Section 10.3, Appendix 3: Regulatory, Ethical, and Study Oversight Considerations for additional details.

Data that may potentially unblind the JNJ-70033093 dose assignment (ie, study drug plasma concentrations, PD and biomarker laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by investigators, the clinical team, or others, as appropriate until the time of database lock and unblinding.

To maintain the blind of the study, the investigator should not measure PD markers (eg, aPTT) locally unless considered necessary for subject clinical care. If performed locally, the results of these laboratory assessments should not be used to determine clinical care. In addition, the investigator will not receive the results of the PD parameters from the central specialty laboratory during the conduct of the study.

6.4. Study Drug Compliance

Drug supplies will be inventoried and accounted for throughout the study. The IWRS will track the study drug dispensed. In addition, the sites will enter the study drug returned by subjects into the IWRS.

Subjects randomly assigned to JNJ-70033093 will be required to return all blister cards at the Day 10-14 visit. For enoxaparin, subjects will be required to return unused study drug at the Day 10-14 visit, at which time study drug accountability will be performed. Start and stop dates and any interruptions will be recorded in the eCRF.

Subjects enrolled at selected sites may use an application on the subject's own smartphone/tablet to confirm study drug administration (JNJ-70033093 capsules only).

6.5. Concomitant Therapy

Only selected therapies taken before the first dose of study drug (eg, tranexamic acid, antiplatelet therapies, and nonsteroidal anti-inflammatory drugs [NSAIDs]) administered up to 7 days before first dose of study drug must be recorded.

Concomitant therapies, except those medications given as part of the surgical procedure, must be recorded throughout the study beginning with start of the first dose of study drug to the final visit.

All pharmacologic therapies (prescription or over-the-counter medications, including products to manage bleeding, vaccines, vitamins, and herbal supplements) concomitant with and different from the study drug must be recorded in the eCRF. All concomitant non-pharmacologic therapies such as intermittent pneumatic compression devices, foot-pump devices, continuous passive motion devices, compression stockings, electrical stimulation, and acupuncture must also be recorded in the eCRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

Study drug must be the first anticoagulant administered after surgery. The following medications/therapies should not be given concomitantly with the study drug:

- Additional anticoagulant(s) (eg, vitamin K antagonists, Factor IIa or FXa inhibitors). The study drug will be discontinued in subjects who develop any condition that requires long-term anticoagulation (eg, DVT, atrial fibrillation)
- Antiplatelet therapies (eg, platelet adenosine diphosphate P2Y12 receptor antagonist [clopidogrel, ticagrelor, prasugrel]), except for aspirin ≤100 mg/day
- Strong CYP3A4/P-gp inhibitors or strong CYP3A4/P-gp inducers in the 7 days before randomization or concomitant use with the study drug (concomitant use with study drug applies only to subjects taking JNJ-70033093)
- Intermittent pneumatic compression after the first postoperative dose of study drug (all mechanical VTE prevention methods such as foot pumps, graduated compression stockings, and continuous passive motion devices are permitted)

Nonsteroidal anti-inflammatory drugs should be avoided, if possible, during the study because their use can increase the risk of bleeding and may interfere with collagen formation. If NSAID use is necessary, it is recommended that the minimum dose is used for the shortest possible duration. If the investigator deems anticoagulation to be indicated after the last dose of study drug, anticoagulation therapy may begin after the venography per standard-of-care.

6.6. Dose Modification

The assigned dose of JNJ-70033093, matching placebo, and enoxaparin will not be modified during the course of the study. Subjects will receive the full dose of study drug on Day 1 and will remain on their assigned dosages throughout the treatment phase (ie, until Day 10-14 or early discontinuation of the study drug).

6.7. Study Drug After the End of the Study

Subjects will be instructed that study drug will not be made available to them after they have completed/discontinued study drug and that they should return to their primary physician to determine standard-of-care.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

It is imperative for the integrity of the study and results to have complete data. If a subject withdraws from the study before the end of the follow-up phase and is unwilling or unable to return for follow-up visits in person or have follow-up contacts, the study-site should collect as much follow-up visit information as possible, including contacting the subject or subject's representative or health care professional by telephone or by email. If applicable, vital status may be obtained by reviewing the subject's medical or public records unless this contact is not permitted per local regulations.

Study drug assigned to a subject that discontinues the study drug or withdraws may not be assigned to another subject. Subjects who withdraw will not be replaced.

7.1. Discontinuation of Study Drug

A subject's study drug must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue the study drug
- Bleeding into a critical site (eg, intracranial, intraspinal, intraocular, pericardial, intra-articular in a nonoperative joint, intramuscular with compartment syndrome, retroperitoneal)
- Drug-induced liver injury meeting the criteria for discontinuation (see Section 8.3.1.3, Liver Enzyme Elevations and Clinical Liver Events)
- Development of any condition that requires open-label treatment with an anticoagulant or other prohibited medication
- The subject requests to discontinue the study drug permanently
- The subject becomes pregnant during the study
- At the (exceptional) request of the sponsor

If a subject discontinues study drug for any reason before the end of the postoperative dosing phase, the assessments should be continued as scheduled.

7.1.1. Temporary Discontinuation

The study drug may be interrupted if a subject develops bleeding or elevated liver enzymes as described in Sections 8.2.1.2, Approach to Subjects With a Bleeding Event and 8.3.1.3, Liver Enzyme Elevations and Clinical Liver Events, respectively.

7.2. Subject Discontinuation/Withdrawal From the Study

A subject will not be automatically withdrawn from the study if he or she has to discontinue study drug before the end of the study drug regimen.

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent

  Withdrawal of consent should be a very unusual occurrence in a clinical study. Subjects who elect to stop the study drug are not automatically considered to have withdrawn consent. The investigator should make every effort to maintain a good relationship with subjects to avoid this occurrence. Withdrawal of consent will be recorded in the eCRF for this study after a discussion between the investigator and the appropriate sponsor representative has taken place.

At the time of signing the ICF, a subject will agree to be contacted to obtain follow-up information should he or she decided to withdraw from the study. If a subject withdraws from the study before the end of the follow-up phase and is unwilling or unable to return for follow-up visits in person or have follow-up contacts, the study-site should collect as much follow-up visit information as possible, including contacting the subject or the subject's representative or health care professional by telephone or by email to determine vital status and to collect medical information related to endpoint events, as agreed to by the subject during the initial informed consent process. For subjects who withdraw consent from study participation, the reasons for the withdrawal of consent should be documented in the source documents and entered in the eCRF. If applicable, vital status may be obtained by reviewing the subject's medical or public records unless this contact is not permitted per local regulations.

For subjects who withdraw consent and are not agreeable to any follow-up contact, it is recommended that the subject withdraw consent in writing, and the subject will be asked to supplement the withdrawal of consent with a signed written statement documenting refusal from all subsequent contact. If the subject refuses or is physically unavailable, the study-site should document and sign the reason for the subject's failure to withdraw consent in writing and maintain it with the subject's source records. If the subject chooses to withdraw from the study completely and does not allow further contact by the investigator, then the investigator or designee will consult sources available in the public domain to check the health status of the subject as permitted by local law.

When a subject withdraws consent before completing the study, it is not required for he/she to give a reason. If the reason for withdrawal is known, it should be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Additional subjects will not be entered. If a subject discontinues study drug and does not withdraw consent from the study before the end, Day 10-14 assessments should be obtained, including the venography of the operated leg (unless a PE or symptomatic proximal DVT has been diagnosed), and the remaining visits through the Week 6 assessments should be completed.

7.2.1. Withdrawal of Consent for the Use of Research Samples

Withdrawal of Consent for the Use of Samples in Future Research

The subject may withdraw consent for use of samples for future research (refer to Long-Term Retention of Samples for Additional Future Research in Section 10.3, Appendix 3, Regulatory,

Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

7.3. Lost to Follow-Up

If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine their status and the reason for discontinuation/withdrawal, including the possible use of locator agencies to determine vital status, as local laws and regulations permit. The measures taken to follow-up must be documented in the subject's source documents. A subject will be considered lost to follow-up only after all means of subsequent contact have been exhausted. Refer to Section 7.2, Subject Discontinuation/Withdrawal From the Study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities summarizes the frequency and timing of efficacy, PK, PD, biomarkers, and safety measurements applicable to this study.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the sequence specified in the central laboratory manual. Blood collections for PK, PD, and biomarker assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints, if needed. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

The total blood volume collected in the study by treatment group is as follows: for the JNJ-70033093 group - approximately 135 mL (20 mL for safety, 20 mL for PK, and 95 mL for PD/biomarkers) and for the enoxaparin group – approximately 115 mL (20 mL for safety, and up to 95 mL for PD/biomarkers).

Additional blood samples may be collected, if necessary, for additional safety, PK, PD, or biomarker assessments based on emerging data, but the maximum amount of blood drawn from each subject in this study will not exceed 200 mL without prior Independent Ethics Committee (IEC) or Institutional Review Board (IRB) and health-authority approvals. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples and do not require prior IEC/IRB and health-authority approvals.

Volume of Blood to be Collected From Each Subject

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Approximate Total Volume of Blood (mL)[a]
Safety (including screening and post-intervention assessments)			
- Hematology	2.0	4	8
- Serum chemistry	2.5	4	10
Serum β-hCG pregnancy tests[b]	2.5	1	2.5
PK samples	2.0	10	20
PD and biomarker samples			
- aPTT and PT	4.5	7	31.5
- TGA	4.5	7	31.5
- FXI clotting activity or anti-FXa activity	1.8	3	5.4
- hs-cTnT	4.0	2	8.0
- FXI antigen	1.8	1	1.8
- Archive sample	2.7	3	8.1
- D-dimer	2.7	3	8.1
Approximate Total[c]			134.9

anti-FXa=anti-Factor Xa; aPTT=activated partial thromboplastin time; β-hCG=beta-human chorionic gonadotropin; FXI=Factor XI; hs-cTnT=high-sensitive cardiac troponin T; No.=number; PD=pharmacodynamics(s); PK=pharmacokinetic(s); PT=prothrombin time; TGA=thrombin generation assay

a. Calculated as the number of samples multiplied by amount of blood per sample.
b. If a serum β-hCG pregnancy test is required, it will be performed by the study-site's local laboratory.
c. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples and are not included in the total volumes.

Note: An indwelling IV cannula may be used for blood sample collection.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF and/or laboratory requisition form. It is important to record the exact date and time for PK sample collection even if the time deviates from the scheduled time of collection. If blood samples are collected via an indwelling cannula, an appropriate amount (eg, 1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (or equivalent) and charged with a volume equal to the dead space volume of the lock.

Refer to the Schedule of Activities for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manuals that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB
- Pharmacy manual/study-site investigational product and procedures manual
- Laboratory manuals for clinical, PK, PD, and biomarker laboratory specimens
- IWRS Manual
- Electronic data capture (eDC) Manual
- Sample ICF
- Venography manual
- Guidelines for reporting bleeding event verbatim terms
- Subject contact cards (wallet card)
- Contact information page

8.1. Efficacy Assessments

Efficacy evaluations will include unilateral venography assessment of the operated leg and assessments of symptomatic DVT, PE, or death to assess the primary, secondary, and exploratory efficacy outcomes.

8.1.1. Assessments for DVT

Venography assessments of the operated leg will be performed by injecting contrast agent into a foot vein and obtaining x-ray images of the proximal and distal leg veins. Evaluable venography assessments require the visualization of all the deep veins except for the muscular, anterior tibial, and deep femoral veins. An ultrasound will be performed in those subjects with suspected symptomatic DVT prior to the Day 10-14 visit. In these cases, if the ultrasound confirms symptomatic proximal DVT, a subsequent venography assessment is not required. If the ultrasound is negative or confirms a distal DVT, the venography assessment should be conducted on the Day 10-14 visit.

Study-specific venography assessment training will be provided to each study-site. Each study-site will be responsible for identifying at least 1 primary person to perform the venography assessments for subjects. Evaluability of the venography assessments based on centrally adjudicated data will be monitored for each site on an ongoing basis. If venography assessment performance is considered not acceptable, then further randomization by the investigator may be suspended until additional training or retraining is provided. Additional details regarding the venography procedure and study-specific training requirements will be provided in a venography manual, which will be provided separately to the study sites.

8.1.2. Assessments for PE

For all subjects with symptoms of PE, spiral computed tomography, pulmonary angiography, or perfusion/ventilation lung scanning combined with chest radiography will be performed. A diagnosis of PE will be made only if the subject has symptoms of PE (eg, sudden onset of dyspnea, chest pain, or fainting), and 1 of the following criteria is met:

- Positive spiral computed tomography scan of the chest revealing a segmental or more proximal thrombus
- Positive pulmonary arteriogram
- High probability ventilation/perfusion lung scan (defined as 1 or more segmental or large [>75% of a segment] subsegmental perfusion defects associated with ventilation mismatch)
- Intermediate probability ventilation/perfusion lung scan and ultrasound or venographic evidence of DVT
- Autopsy confirmation

If a subject is objectively diagnosed with a PE meeting the specified definitions prior to Day 10-14, a subsequent venography assessment of the operated leg is not required.

8.2. Safety Assessments

The safety and tolerability of JNJ-70033093 will be evaluated throughout the study according to the timepoints provided in the Schedule of Activities by the assessment of adverse events, including nonserious adverse events, serious adverse events, adverse events of interest (ie, bleeding events, liver enzyme elevations and clinical liver events, and wound or joint complications), clinical laboratory tests (ie, hematology, clinical chemistry, urinalysis), and physical examinations. All bleeding events will be classified according to the definitions of bleeding events in Section 10.6, Appendix 6, Definition of Bleeding Events. Safety evaluations may also be performed at unscheduled timepoints, if deemed by the investigator or appropriate designee as necessary to ensure the safety of the subject. All suspected symptomatic efficacy events (VTE) will also be captured as adverse events of interest.

The OC will be responsible for reviewing ongoing safety and efficacy data by unblinded subject treatment assignments approximately every 3 to 8 weeks on a periodic basis. They will also review the interim analysis data and make dose decisions, including but not limited to deciding whether to proceed with the optional dose regimen and at what dose(s). Details regarding the OC are provided in Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events and Serious Adverse Events and Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the adverse event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities.

8.2.1. Bleeding Events

8.2.1.1. Classification of Bleeding Events

All subjects will be observed for signs and symptoms of bleeding events throughout the study and at each study visit as indicated in the Schedule of Activities.

The investigator's classification of bleeding events according to the protocol classification will be collected in the eCRF (Section 10.6, Appendix 6, Definition of Bleeding Events). Additional information, including but not limited to the list below, will be collected for subjects with bleeding events and captured in the source documents and entered into the eCRF:

- Location of the bleeding and duration
- Provocation of the bleeding
- Association with any procedure
- Action taken regarding the study drug
- Concomitant or additional treatment given for this bleeding event
- Any associated hemoglobin (and/or hematocrit) levels
- Hospitalization (or prolonged hospitalization) due to bleeding events
- Outcome

All available information related to the classification of bleeding events will be collected and adjudicated by the independent CEC.

8.2.1.2. Approach to Subjects With a Bleeding Event

If a subject has a bleeding event requiring intervention during the study, the following measures should be considered:

- Discontinue the study drug (refer to Section 7.1, Discontinuation of Study Drug)
- Usual treatment measures for bleeding events, including local pressure, fluid replacement and hemodynamic support, blood transfusion, and fresh frozen plasma, if physical examination and laboratory testing suggest that benefit could be obtained
- Other causes besides antithrombotic medication can be contributory to the seriousness of the bleeding event (ie, rule out disseminated intravascular coagulation, thrombocytopenia, and other coagulopathies, kidney and liver dysfunction, concomitant medications) and should be treated accordingly
- Depending on local availability, consultation with a coagulation expert should be considered

Currently, there is no reversal agent for JNJ-70033093; however, the anticoagulant effect of JNJ-70033093 dissipates in 48 to 72 hours. At therapeutic doses, the anticoagulant effects of JNJ-70033093 will not be reflected by international normalized ratio (INR) values but may be reflected by prolongation of aPTT. In-vitro spiking of human plasma with JNJ-70033093 resulted in concentration-dependent increases in aPTT, which is consistent with its mechanism of action. Pre-incubation with activated 4-factor prothrombin concentrate complex (FEIBA) and Factor VIIa (Novo-Seven®), 2 commercially available nonspecific reversal agents, were able to prevent JNJ-70033093-induced prolongations in aPTT. These data demonstrate that FEIBA (and Factor VIIa by bypassing FXIa inhibition), can promote clotting and provide hemostasis.[9] Furthermore, FEIBA was able to reverse bleeding induced by a FXIa-inhibitor compound in a rat-tail transection model of bleeding in anesthetized rats.[10] Also, in FXI-deficient patients, recombinant Factor VIIa has been used successfully to prevent surgical bleeding without complication.

Therefore, if bleeding cannot be controlled by these measures, administration of FEIBA or Factor VIIa according to the dosages and dosing schedules that are recommended in their respective package inserts could be considered (Note: consultation with a coagulation expert is recommended before use).

Protamine sulfate partially reverses the anticoagulant activity of enoxaparin. For subjects receiving enoxaparin, if bleeding cannot be controlled by the above measures protamine can be considered at the dosages recommended in the SmPC.

8.2.2. Physical Examination

The physical examination consists of a routine medical examination that includes general appearance and a review of the following systems: neurologic, eyes/ears/nose/throat, thyroid, cardiovascular, respiratory, abdominal/gastrointestinal, hepatic, musculoskeletal, and dermatologic. Any bleeding observed during the examination (eg, skin, gingiva, nares) will be recorded as a potential bleeding event as described in Section 8.2.1.1, Classification of Bleeding Events. Additional body systems or further detailed physical examinations (eg, rectal examinations) should be performed if considered clinically appropriate by the investigator. Physical examinations will be performed by the investigator or a designated health care professional who is licensed and/or certified in accordance with applicable local laws to perform physical examinations.

Height and weight should be obtained at the screening visit, with weight only on the final visit.

The physical examination will be conducted at the time points indicated in the Schedule of Activities. An assessment of the wound will be made at all visits as part of the adverse event assessment. Any new, clinically significant findings (in the opinion of the investigator) that were not noted at the time of the screening visit must be captured as adverse events and will be followed to resolution.

8.2.3. Vital Signs

Vital signs measurements are not being collected in this study.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be collected as noted in Section 10.2, Appendix 2, Clinical Laboratory Tests. The investigator or appropriate designee must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

At screening, the investigator will need to determine that the subject is medically appropriate for anticoagulant prophylaxis on the basis of clinical laboratory tests performed as part of local standard-of-care as part of screening for elective TKR surgery. Hematology and chemistry laboratory tests and a urine sample for urinalysis will be obtained before dosing (0 hour) and will be performed by the central laboratory. Refer to Section 10.2, Appendix 2, Clinical Laboratory Tests for the list of tests to be performed by the central laboratory.

8.3. Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study.

There are no anticipated events in this study. Since this is one of the first studies to evaluate JNJ-70033093 in subjects, all adverse events and serious adverse events are important in understanding the safety of the study drug and will be collected for the duration of the study.

For further details on adverse events and serious adverse events (Definitions and Classifications; Attribution Definitions; Severity Criteria; Special Reporting Situations; Procedures) as well as product quality complaints, refer to Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.1. Adverse Events of Interest

Investigators will be asked to provide more detailed information in the source documents and the applicable eCRF forms for adverse events of interest that are considered to be one of the following:

- Bleeding events
- Wound or joint complications

- Liver enzyme elevation and clinical liver events

  Note: As previously noted in Section 8.2, Safety Assessments, all suspected symptomatic efficacy events (VTE) will also be captured as adverse events of interest. Asymptomatic DVT found on the planned Day 10-14 venography assessment does not need to be reported as an adverse event unless it meets the criteria for a serious adverse event (eg, prolonged hospitalization). Information from these asymptomatic events will be reported on the venography assessment eCRF.

8.3.1.1. Bleeding Events - Adverse Events of Interest

Refer to Section 8.2.1, Bleeding Events, for further details on the classification of bleeding events as well as the approach to use with subjects who present with a bleeding event.

8.3.1.2. Wound or Joint Complications

All subjects will be observed for signs and symptoms of wound or joint complications throughout the study and at each study visit as indicated in the Schedule of Activities. The wound will be evaluated by the investigator for any abnormal bleeding, swelling, redness, drainage, or infection. Any joint complications such as bleeding/hematoma, infection or prosthesis malfunction (eg, limited range of motion) will also be recorded as adverse events of interest. Any medical or surgical treatments for wound or joint complications will be recorded as well.

8.3.1.3. Liver Enzyme Elevations and Clinical Liver Events

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur before the reporting of a potential drug-induced liver injury. Subjects meeting the following criteria for liver-related laboratory abnormalities for all cases must be reported as adverse events of interest and have study drug discontinued immediately:

- ALT and/or AST ≥5x the upper limit of normal (ULN) for ≥7 consecutive days, confirmed by repeat
- ALT and/or AST ≥10x ULN, confirmed by repeat*
- Potential drug-induced liver injury (as defined below)

The following is not required to be reported as an adverse event of interest but treatment with the study drug should be interrupted if:

- ALT and/or AST ≥3x ULN, confirmed by repeat*

*NOTE: If the ALT and/or AST elevation occurs within 1 calendar day of surgery and the repeat to confirm the elevation is lower than the initial elevation, with the repeat testing performed at least 24 hours after the first sample, the investigator should exercise clinical judgement to determine if the study drug should be immediately discontinued or interrupted. The value should be checked every 48 to 72 hours and if it continues to decrease the study drug can be continued.

Subjects with abnormal liver function tests should be followed until the ALT/AST returns to <2x ULN or to baseline prior to considering the restart of treatment with the study drug, but no later than the scheduled Day 10-14 visit.

A potential drug-induced liver injury is defined as:

- ALT or AST elevation ≥3x ULN

  AND

- Total bilirubin ≥2x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

  AND

- No other immediately apparent possible causes of transaminase elevation and hyperbilirubinemia, including but not limited to: viral hepatitis, preexisting chronic or acute liver disease, or the administration of other drug(s) known to be hepatoxic
- In addition to discontinuing study drug and reporting all potential drug-induced liver injury as adverse events of interest.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury event. All occurrences of potential drug-induced liver injury events, meeting the defined criteria, must be reported as serious adverse events.

8.3.2. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All adverse events and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study-site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

8.3.3. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events

Solicited adverse events are predefined local and systemic events for which the subject is specifically questioned. In this study, subjects will be queried directly to solicit potential bleeding events using general questions about any bleeding and specific questions about common minor bleeding events that could be overlooked by the subject (eg, bruising, gingival bleeding, epistaxis).

Unsolicited Adverse Events

Unsolicited adverse events are all adverse events for which the subject is not specifically questioned.

8.3.4. Follow-Up of Adverse Events and Serious Adverse Events

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.4, Appendix 4, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.5. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs as per regulatory requirements to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified. The determination of the expectedness in the SUSARs will use the IB for JNJ-70033093 and the SmPC for enoxaparin.

8.3.6. Pregnancy

All initial reports of pregnancy in all female subjects or partners of male subjects randomly assigned to JNJ-70033093 must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. If a subject becomes pregnant during the study, the subject must be discontinued from further study intervention.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.4. Treatment of Overdose

For this study, the accidental or intentional administration of any dose of JNJ-70033093 or enoxaparin that is considered both excessive and medically important by the investigator will be considered an overdose and should be reported as a serious adverse event (medically important event). The sponsor does not recommend specific intervention for an overdose (consult the approved product information for enoxaparin). There is no known antidote for overdose with JNJ-70033093 and no studies have been performed to assess methods of reversing JNJ-70033093 absorption effects; however, in theory, activated charcoal may reduce the absorption of JNJ-70033093 if given early after administration of JNJ-70033093.

In the event of an overdose with JNJ-70033093, the investigator or treating physician should:

- Contact the Medical Monitor listed in the Protocol Contact Page immediately.
- Closely monitor the subject for adverse event/serious adverse event and laboratory abnormalities until JNJ-70033093 can no longer be detected systemically (at least 2 days).
- Monitoring aPTT may be of help in determining the extent of anticoagulation.
- Obtain plasma samples for PK and PD (aPTT and PT) analysis as soon as possible from the date of the last dose of study drug if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose (number of capsules), the nature (accidental, intentional) as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

8.5. Pharmacokinetics

Plasma samples will be used to evaluate the PK of JNJ-70033093. Plasma collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these plasma samples. Subject confidentiality will be maintained.

8.5.1. Evaluations

Venous blood samples of approximately 2 mL will be collected and divided into 2 aliquots for measurement of plasma concentrations of JNJ-70033093. All samples should be timed from the first postoperative dose taken. The dosing date and time of each dose of JNJ-70033093 on the preceding day will also be recorded in the eCRF. Subjects who experience a suspected bleeding event or symptomatic thrombotic event should have PK samples collected as soon as practically possible after the event occurs.

Samples collected for analyses of JNJ-70033093 plasma concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period for the evaluation of relevant biomarkers. Additional information about the collection, handling, and shipment of biological samples can be found in the PK Laboratory Manual.

8.5.2. Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of JNJ-70033093 using a validated, specific, and sensitive (eg, liquid chromatography-mass spectrometry/mass spectrometry) method by or under the supervision of the sponsor. Pharmacokinetic samples will be collected from all subjects randomly assigned to JNJ-70033093. Detailed instruction for the PK blood collection, labeling, processing, storage, and shipping will be provided to the study-site in the procedures manual.

In addition, residual plasma PK samples may be stored for future analysis of the metabolite profile, if needed. If these analyses are conducted, they will be reported separately from the CSR.

The Schedule of Activities lists the sampling schedule to be followed for the assessment of PK. In addition to the times listed in the table, a sample for measurement of JNJ-70033093 plasma concentration should be collected as close to practically possible for any subject who experiences a suspected symptomatic thrombotic or bleeding event, or if requested by the Medical Monitor (determined on a case-by-case basis) in the event of an overdose.

8.5.3. Pharmacokinetic Parameters and Evaluations

Parameters

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters (eg, apparent clearance, apparent volume of distribution) and exposure for exposure-response analysis of JNJ-70033093 and associated variables will be derived using population PK modeling. Baseline covariates (eg, body weight, age, sex, creatinine clearance, race) may be included in the model, if relevant. The analysis of these parameters will be outlined in the population PK modeling plan and reported separately from the CSR.

Pharmacokinetic/Pharmacodynamic Evaluations

The relationship between the observed plasma concentration of JNJ-70033093 and measured PD markers will be investigated graphically. If appropriate, PK/PD exposure and response-relationships may be further analyzed quantitatively.

The relationships between the plasma PK exposure of JNJ-70033093 derived from the population PK model will be correlated with the measured PD markers and safety/efficacy endpoints via graphical analysis. When necessary, these data may be analyzed statistically using a suitable model. The details of the analyses plan will be presented in a population PK modeling plan that is separated from the Statistical Analysis Plan (SAP). The results will be reported separately from the CSR.

8.6. Pharmacodynamics

Venous blood samples will be collected for PD evaluation of aPTT, PT, FXI clotting activity, anti-FXa activity, and TGA at the timepoints specified in the Schedule of Activities. Factor XI

clotting activity will be assessed in subjects randomly assigned to JNJ-70033093 and anti-FXa activity will be assessed in subjects randomly assigned to enoxaparin. Subjects who experience a suspected bleeding event or symptomatic thrombotic event should have PD samples collected as soon as practically possible after the event occurs. Additional information about the collection, handling and shipment of biological samples can be found in the PD laboratory manual.

Activated Partial Thromboplastin Time

Activated partial thromboplastin time is a measure of the intrinsic and final common pathways of the coagulation cascade. It represents the time, in seconds, for plasma to clot after addition of phospholipid, an intrinsic pathway activator, and calcium. The name 'Activated Partial Thromboplastin Time' comes from the original form of the test in which only the phospholipid concentration of the test was controlled (as opposed to the phospholipid and the surface activator concentrations) and the name 'partial thromboplastin' was applied at the time to phospholipid preparations that accelerated clotting but did not correct the prolonged clotting times of hemophilic plasma. The term 'partial' means phospholipid is present but no tissue factor. The normal and reference ranges vary depending on reagent and instrument combinations, particularly with the phospholipid composition. It is used to evaluate the coagulation Factors XII, XI, IX, VIII, X, V, II (prothrombin), and I (fibrinogen) as well as prekallikrein and high molecular-weight kininogen. Heparin, DOACs, and direct thrombin inhibitors, including hirudin, argatroban, and dabigatran have an effect on the assay. Blood will be collected for measurement of changes in aPTT clotting time.

Prothrombin Time

Prothrombin time is a global clotting test that is used for the assessment of the extrinsic pathway of the blood coagulation cascade. It is a 1-stage test based upon on the time required for a fibrin clot to form after the addition of tissue factor (historically known as tissue thromboplastin), phospholipid, and calcium to decalcified, platelet-poor plasma. The test is sensitive for deficiencies of fibrinogen and Factors II, V, VII, and X, with sensitivity being best for Factors V, VII, and X and less pronounced for Factor II. Prothrombin time and the normalized version, INRs are used to monitor warfarin therapy. It should be noted that currently, 3 types of PT reagents are used: recombinant thromboplastins, tissue thromboplastins (which are usually from rabbit brain or human placenta), or combined thromboplastins (tissue thromboplastin diluted into fibrinogen). These reagents differ in factor sensitivity, heparin responsiveness, lot-to-lot consistency, and absolute value of the clotting times.

Factor XI Clotting Activity

Factor XI clotting activity is determined utilizing an aPTT-based 1-stage clotting time assay. Serial dilutions of normal pooled plasma are mixed with FXI-depleted plasma and the clotting times are measured according to standard aPTT protocol, to establish a reference range. Subject test plasma is treated in the same way and compared with the reference plasma. The assay will be performed at a specialty laboratory.

Anti-Factor Xa Activity

The plasma anti-FXa assay is used to monitor factor unfractionated heparin and LMWH. The plasma anti-FXa assay provides an accurate assessment of LMWH activity. Factor Xa is added to plasma containing a FXa-specific substrate and substrate hydrolysis is measured. A standard curve is generated by measuring the FXa chromogenic activity in control plasma samples that contain known concentrations of LMWHs. Chromogenic activity in patient plasma is then compared to the standard curve to determine the LMWH level.

Thrombin Generation Assay

The TGA is a global coagulation assay that evaluates the thrombogenic capacity of a plasma sample and has been proposed that it may better reflect prothrombotic or hemorrhagic states than conventional clotting assays. In the traditional TGA, coagulation of citrated plasma is initiated through the extrinsic pathway by adding tissue factor, phospholipids, and calcium. For this study, a kaolin slurry will be used instead to initiate coagulation through the contact activation pathway. Using this approach, a Factor XI-specific TGA can also be performed by diluting test plasma into FXI-deficient plasma and measuring kaolin-induced thrombin generation, similar to the approach used for FXI-specific clotting. Thrombin generation is continuously monitored through the product released by cleavage of a thrombin-specific fluorogenic substrate. The generated thrombogram is used to determine several relevant parameters, including endogenous thrombin potential, defined as the net amount of thrombin that test plasmas can generate based on the relative strength of the pro- and anticoagulant reactions.

Archive Sample for Exploratory Research

Blood samples will be collected at the time points specified in the Schedule of Activities and a plasma sample archived for future exploratory PD research related to the safety and/or efficacy of JNJ-70033093. Refer to the PD laboratory manual for detailed instructions for sample collection, processing and shipment of archive samples for exploratory research.

8.7. Biomarkers

Venous blood samples will be collected for measurement of D-dimer, high-sensitive cardiac troponin T (hs-cTnT), and FXI antigen assessment at the timepoints specified in the Schedule of Activities.

D-dimer

The various states of coagulation activation that occur in vivo lead to the production of thrombin and then, cross-linked fibrin. What follows is a reactive fibrinolysis, during which plasmin breaks down fibrin. D-dimer is the ultimate degradation product of cross-linked fibrin. The presence of D-dimer in plasma is an indirect marker of a coagulation activation followed by a reactive thrombolysis. Increased levels D-dimer can be found in patients with DVT, PE, disseminated intravascular coagulation, hemorrhages, surgery, cancers, and severe infections. The D-dimer assay is an enzyme immunoassay procedure for the quantitative determination of D-dimer levels.

High-sensitive Cardiac Troponin T

The troponin complex, consisting of troponin C, T, and I subunits, regulates the contraction of striated muscles. Damage to cardiac muscle tissue causes release of troponins into the bloodstream and circulating troponin levels correlate to the degree of muscle damage; accordingly, cardiac troponins are considered primary biomarkers for diagnosis of acute MI and risk assessment in acute coronary syndrome. Immunoassays are performed to detect cardiac troponin T in plasma samples prepared from venous blood collection.

Factor XI Antigen

Measurement of FXI antigen in plasma at baseline, using a validated immunoassay, may help to improve understanding of thrombotic conditions and help identify subjects susceptible to cardiovascular events.

8.8. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

This study will use an adaptive design intended to optimize data collection for dose-response modeling. It is estimated that approximately 900 subjects will be randomly assigned to treatment in this study, with an option to increase to approximately 1,200 subjects based on the possible addition of once daily dose groups, and/or evaluability rate. Initially, subjects will be randomly assigned to BID doses of JNJ-70033093 25, 50, 100, and 200 mg and enoxaparin 40 mg once daily in a 1:1:1:1:2 randomization ratio. Unblinded periodic and interim analyses will be conducted by the OC for the purposes of safety oversight and as part of the adaptive approach. Periodic reviews will be conducted every 3 to 8 weeks and the first interim analysis, will occur when approximately 300 subjects will have completed the venography or have had a symptomatic VTE event. The dose regimens and randomization ratio may be adjusted post-analyses, depending on the analysis results and safety review. These adjustments include dropping ineffective dose regimens or dose regimens with safety concerns (especially bleeding) as well as adding dose regimens (ie, once daily dose regimen). The randomization ratio may be modified to optimize data collection for dose-response estimation.

9.1. Sample Size Determination

Assuming the evaluability rate (rate of subjects with a valid assessment of potential efficacy outcome and who take at least 1 dose of study drug) is 80%, if the true underlying total VTE event rates are as shown in Table 2, the study is expected to have over 99% power to declare proof-of-efficacy at a 1-sided, 5% α-level. Proof-of-efficacy is defined as either a statistically significant dose-response trend or primary endpoint event rate for the combined BID JNJ-

70033093 groups that is statistically lower than 30%. The exact power will vary because of the nature of the adaptive study design.

Comparison with enoxaparin will be based on the comparison between the highest postoperative dose with acceptable safety and enoxaparin. For example, if the highest dose for acceptable safety is 200 mg BID, the number of evaluable subjects at this dose and enoxaparin groups is expected to be 120 and 240 subjects respectively, the power to detect a statistically significantly lower total VTE event rate against enoxaparin, at 1-sided, 5% α-level, is over 90%.

Table 2: Assumed Total VTE Event Rates by Treatment Group in Sample Size Determination

	JNJ-70033093				Enoxaparin 40 mg once daily
	25 mg	50 mg	100 mg	200 mg	
BID	18%	14.5%	12.5%	11.0%	
Once daily		24%		14%	23.8%

BID=twice daily VTE=venous thromboembolism

9.2. Populations for Analyses

For purposes of analysis, the following populations are defined in Table 3:

Table 3: Analysis Populations

Population	Description
ITT	(as termed Full Analysis Set in the ICH E9 guideline): This population consists of all randomized subjects who have a signed informed consent.
mITT	This population is a subset of the ITT population, consisting of subjects who take at least 1 dose of the study drug and have a valid assessment of potential efficacy outcome at the Day 10-14 visit.
Safety	This population is a subset of the ITT population, consisting of subjects who receive at least 1 dose of the study drug.

ICH=International Conference on Harmonisation; ITT=intent-to-treat; mITT=modified intent-to-treat

The valid assessment of potential efficacy outcome is defined as subjects meeting 1 of the following.

- Had an evaluable venography at the Day 10-14 visit
- Had symptomatic DVT or PE at the Day 10-14 visit and the Week 6 visit
- Died before the Day 10-14 visit and before the Week 6 visit

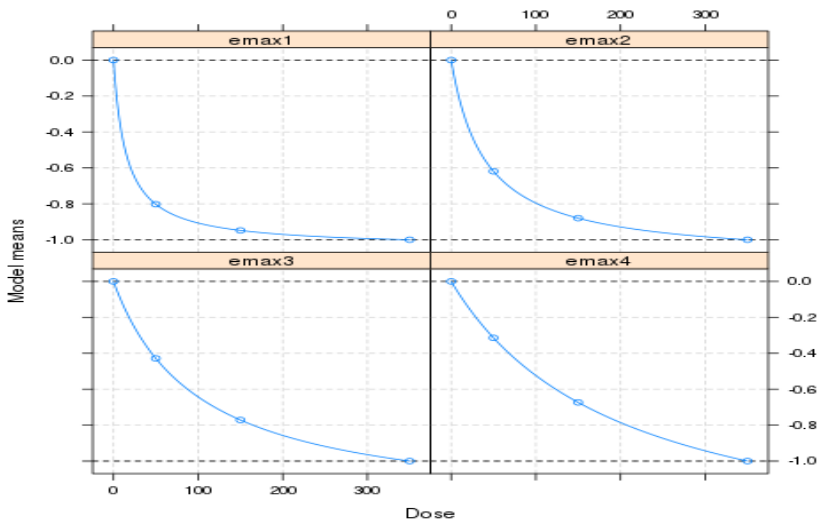
9.3. Statistical Analyses

9.3.1. Efficacy Analyses

The study objectives include proof-of-efficacy and estimation of dose-response relationship in total VTE. The dose-response trend and estimation of dose-response relationship will be addressed by a unified (modified) MCP-Mod approach,[1,3,30] utilizing collective data from postoperative regimens. Proof-of-efficacy will be established by either a statistically significant dose-response trend, or by a statistically lower total VTE event rate in combined BID data

compared with 30%. The rate of 30% is a conservative estimate of the total VTE rate in subjects given placebo. The trend test consists of contrast tests defined by prespecified candidate models (4 E_{max} dose-response modules with varying degrees of ED_{50}, Figure 4), which provide estimates of dose-response (taking BID and once daily into consideration).

Figure 4: Canonical Candidate E_{max} Dose-response Models Used in the MCP-Mod Analysis



The efficacy of the drug is established when the maximum of the t-test statistics for the dose-response trend exceeds the critical value. Predicted event rates at a specific dose will be derived for the candidate model.

The details of the adaptive decision guidelines will be specified in the OC charter and the SAP.

The primary analyses of efficacy endpoints will be based on CEC-adjudicated events from the mITT population. Subjects who do not receive any study drug will be excluded from the primary analysis. However, they will be included in sensitivity analyses as defined in the SAP. The primary efficacy endpoint and its components will be summarized by dose and treatment group. Prespecified clinical variables of interest for the efficacy subgroup analyses include region, age, sex, body mass index, renal function, surgery duration, and tourniquet use.

9.3.2. Safety Analyses

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Study drug-emergent adverse events are adverse events with onset during the postoperative dosing phase or that are a consequence of a preexisting condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summaries, listings, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue the study drug due to an adverse event, or who experience a severe or a serious adverse event.

Adverse events of interest that will be counted or listed are bleeding events, wound or joint complications, and liver enzyme elevations and clinical liver events.

The safety population will be a subset of the ITT population consisting of subjects who take at least 1 dose of the study drug. The analyses of bleeding adverse events will be based on the CEC-adjudicated events; all other nonefficacy or nonbleeding adverse events will be based on investigator-reported events in the safety population.

Estimation of the dose-response relationship in any bleeding will be addressed by a unified (modified) MCP-Mod approach as with efficacy. Any bleeding, major bleeding, clinically relevant nonmajor bleeding, composite of major or clinically relevant nonmajor bleeding, and minimal bleeding will be summarized by the dose and treatment group. The same variables specified for the efficacy subgroup analyses will be used for the safety subgroup analysis with the addition of aspirin/nonsteroidal anti-inflammatory drugs.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Physical Examination

Height and weight will be summarized.

9.3.3. Other Analyses

Pharmacokinetic Analyses

Population PK analysis of plasma concentration-time data of JNJ-70033093 will be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline subject characteristics (ie, demographics, laboratory variables, genotypes, race) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Data will be listed for all subjects with available plasma concentrations per treatment group. Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study intervention; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All subjects and samples excluded from the analysis will be clearly documented in the study report.

For each treatment group, descriptive statistics, including arithmetic mean, standard deviation (SD), coefficient of variation, median, minimum, and maximum will be calculated for all individual derived PK parameters including exposure information of JNJ-70033093.

All plasma concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations or SAS dataset. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the CSR.

Descriptive statistics will be used to summarize JNJ-70033093 plasma concentrations at each sampling time point.

Exposure-response analyses will be conducted to explore the relationship of the plasma concentration of JNJ-70033093 with efficacy and safety endpoints. The details of the analyses plan will be presented in a population PK modeling plan that is separate from the SAP. The results will be reported separately from the CSR.

Pharmacodynamic and Biomarker Analyses

Descriptive statistics, including mean, median, SD, minimum, and maximum will be provided for the percent change from baseline of the PD (aPTT, PT, FXI clotting activity, anti-FXa activity, TGA) and biomarker (D-dimer, hs-cTnT) parameters by nominal time of collection and dose and regimen level. The parameters may be statistically analyzed using mixed models. FXI antigen levels will be summarized.

Pharmacokinetic/Pharmacodynamic Analyses

The relationship between observed plasma concentration of JNJ-70033093 and measured PD markers will be investigated graphically. If appropriate, PK/PD exposure and response relationships may be further analyzed quantitatively.

The relationship between the plasma PK exposure of JNJ-70033093 derived from the population PK model will be correlated with the measured PD markers and safety/efficacy endpoints via graphical analysis. When necessary, these data may be analyzed statistically using a suitable model. The details of the analyses plan will be presented in a population PK modeling plan that is separate from the SAP. The results will be reported separately from CSR.

9.4. Periodic and Interim Analyses

Unblinded periodic and interim analyses will be conducted by the OC for the purposes of safety oversight and as part of the adaptive approach. The interim analysis will be triggered when approximately 300 subjects (approximately 50 subjects in each of the JNJ-70033093 BID treatment groups) will have completed the venography or have had a symptomatic VTE event. Both periodic and interim analyses results will be used to guide the decision to drop doses of

JNJ-70033093 and/or adjust the randomization ratio. The number of subjects who were planned to be randomized into the dropped dosing regimen can be allocated to one of the other active dosing groups. The interim analysis will also serve as the formal venue to assess study status and possibly add once daily dosing of 50 mg and/or 200 mg of JNJ-70033093 based on available efficacy and safety data. If PK/PD analysis results are available at the time of the interim analysis, the results will be included in the review. Additional interim analyses will be conducted, as needed, at the discretion of the OC. A futility analysis will also be included as part of the interim analysis, which may lead to stopping the entire study. These decisions will be made only after taking the safety and efficacy profiles of JNJ-70033093 into account. Further details related to the first interim analysis and any subsequent interim analyses as determined to be appropriate by the OC as well as the decision guidelines will be specified in the OC charter.

9.4.1. Committees

An OC, Steering Committee, and independent CEC will be established as noted in Committees Structure in Section 10.3, Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ALT	alanine aminotransferase
anti-FXa	anti-Factor Xa
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24h}	area under the concentration versus time curve from 0 to 24 hours of the last measurable concentration
β-hcg	beta-human chorionic gonadotropin
BID	twice daily
BMS	Bristol-Meyers Squibb Company
CEC	Clinical Events Committee
CI	confidence interval
C_{max}	maximum plasma concentration
CSR	clinical study report
CYP	cytochrome P450
DDI	drug-drug interaction
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
ECAT	electrically induced carotid artery thrombus
eCRF	electronic case report form
eDC	electronic data capture
ESRD	end-stage renal disease
FSH	follicle stimulating hormone
FXa	Factor Xa
FXI	Factor XI
FXIa	Factor XIa
GCP	Good Clinical Practice
hs-cTnT	high-sensitive cardiac troponin T
IB	Investigator's Brochure
IC_{50}	concentration at which 50% inhibition was observed
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web response system
K_i	inhibition constant
LMWH	low molecular-weight heparin
MATE	multidrug and toxin extrusion
MCP-Mod	multiple comparison procedures and modeling
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MINS	myocardial injury in noncardiac surgery
mITT	modified intent-to-treat
MRP	multiple drug-resistance protein
NSAID	nonsteroidal anti-inflammatory drug
NTCP	sodium-taurocholate cotransporting polypeptide
NOAEL	no observed adverse effect level
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
OC	Operations Committee
OCT	organic cation transporter

PD	pharmacodynamic(s)
PE	pulmonary embolism
P-gp	p-glycoprotein
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PROBE	prospective, randomized, open-label, blinded endpoint
PT	prothrombin time
RBC	red blood cell
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
TGA	thrombin generation assay
TKR	total knee replacement
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
UV	ultraviolet
VTE	venous thromboembolism
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman of childbearing potential
x	times

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	Red Blood Cell (RBC) Indices: MCV MCH % Reticulocytes	White Blood Cell (WBC) (Complete Blood Count) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.		
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen (BUN) Creatinine Glucose, nonfasting AST/Serum glutamic-oxaloacetic ALT/Serum glutamic-oxaloacetic Gamma-glutamyltransferase (GGT)	Total bilirubin Direct bilirubin (if total bilirubin >2x ULN) Alkaline phosphatase Lactic acid dehydrogenase (LDH) Uric acid Calcium Phosphate Albumin Total protein Cholesterol Triglycerides Magnesium	
	Note: Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.3.1.3, Liver Enzyme Elevations and Clinical Liver Events.		
Routine Urinalysis	Dipstick Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	Sediment (if dipstick result is abnormal) RBCs WBCs Epithelial cells Crystals Casts Bacteria	
	If dipstick result is abnormal, flow cytometry will be used to measure sediment. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.		

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study-site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the principal investigator, where required.
- Signed and dated Clinical Trial Agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable

- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1, Study-Specific Ethical Design Considerations.

FINANCIAL DISCLOSURE

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

INFORMED CONSENT PROCESS

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity and prior to TKR surgery. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for their surgery or postoperative care. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without

violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, which includes permission to obtain information about his or her survival status.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject is obtained.

DATA PROTECTION

Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory PD, biomarker, and PK research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

LONG-TERM RETENTION OF SAMPLES FOR ADDITIONAL FUTURE RESEARCH

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand JNJ-70033093, to understand thrombosis, to understand differential intervention responders, and to develop tests/assays related to JNJ-70033093 and VTE prophylaxis. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal of Consent for the Use of Research Samples).

COMMITTEES STRUCTURE

Operations Committee

An OC will be established for this study. The OC, consisting of clinicians with expertise in thrombosis, thromboprophylaxis, hematology, orthopedic surgery, and clinical studies, and also including clinical and biostatistics representatives from the sponsor (not directly involved in study monitoring), will review ongoing unblinded safety and efficacy data. The OC will be responsible for:

- Reviewing ongoing safety and efficacy data by unblinded subject treatment assignments approximately every 3 to 8 weeks on a periodic basis
- Reviewing the interim analysis data and making dose decisions, including but not limited to deciding whether to proceed with optional dose regimen and at what dose(s)

The details of the OC function and composition, as well as dose decision guidelines will be described in the OC charter.

Steering Committee

A Steering Committee with expertise in thrombosis, thromboprophylaxis, hematology, orthopedic surgery, and clinical studies will be commissioned to provide scientific leadership the study. The Steering Committee will be responsible for providing advice to the sponsor in an effort to ensure the scientific validity and integrity of the study and for the publication of results. The Steering Committee will receive recommendations from the OC regarding suggested modifications to the study based on the review of the unblinded data by the OC. The sponsor, in collaboration with the Steering Committee, will ultimately decide whether to accept the recommendations and will oversee the implementation of any modifications, if applicable. Details regarding the composition, roles, and responsibilities of the Steering Committee will be documented in a separate charter.

Independent Clinical Events Committee

An independent CEC will be established to review, adjudicate, and classify endpoint events as they become available in a blinded, consistent, and unbiased manner according to the definitions

provided in the CEC charter. Committee members will not have direct operational responsibilities for the conduct of the study, nor will they directly enroll subjects or be involved in study monitoring. Further details regarding the composition, roles, and responsibilities of the CEC will be documented in a separate charter.

The CEC will have responsibility for reviewing, adjudicating, and classifying the following assessments and study endpoint events or events that appear suggestive of a study endpoint event:

- Venography assessment
- Suspected symptomatic DVT
- Suspected symptomatic PE
- Suspected bleeding events
- Death

The CEC will verify all components of the bleeding and efficacy endpoint events. The CEC will centrally adjudicate all clinical events based on the endpoint definitions. The CEC will remain blinded to treatment assignment. All necessary source documents will be sent to the CEC in a blinded fashion to enable adjudication and verification of events. The CEC-adjudicated and investigator-reported results on efficacy and safety outcomes will be provided for the interim analysis. The CEC-adjudicated events will be used in the final analysis.

PUBLICATION POLICY/DISSEMINATION OF CLINICAL STUDY DATA

All information, including but not limited to information regarding JNJ-70033093 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-70033093, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a CSR generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of PK, PD, and biomarker analyses performed after the CSR has been issued will be reported in a separate report and will not require a revision of the CSR.

Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study-site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study-site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

DATA QUALITY ASSURANCE

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

CASE REPORT FORM COMPLETION

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

SOURCE DOCUMENTS

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study-site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

MONITORING

The sponsor will use a combination of monitoring techniques: central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study-site visit log that will be kept at the study-site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study-site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

ON-SITE AUDITS

Representatives of the sponsor's clinical quality assurance department may visit the study-site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

STUDY AND SITE CLOSURE

Study Termination

The sponsor reserves the right to close the study-site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study-site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study-site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

ADVERSE EVENT DEFINITIONS AND CLASSIFICATIONS

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.2, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death.
- Is life threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is a suspected transmission of any infectious agent via a medicinal product.
- Is Medically Important.*

*Medical and scientific judgement should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must

be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-70033093, the expectedness of an adverse event will be determined by whether or not it is listed in the IB. For enoxaparin, the expectedness of an adverse event will be determined by whether or not it is listed in the SmPC.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed below (see Attribution Definitions).

ATTRIBUTION DEFINITIONS

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant treatment(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant treatment(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant treatment(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant treatment(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

SEVERITY CRITERIA

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgement in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

SPECIAL REPORTING SITUATIONS

Safety events of interest on a sponsor study drug in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

PROCEDURES

All Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number

- Subject number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a subject in a study through Week 6, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

CONTACTING SPONSOR REGARDING SAFETY

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators,

and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 8.3.2, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Subjects must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.6, Pregnancy, and Section 10.4, Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT (**PREFERRED** METHOD FOR COMPOUNDS WITH POSSIBLE OR UNKNOWN TOXICITY AND **RECOMMENDED** METHOD FOR COMPOUNDS WITH SUSPECTED OR DEMONSTRATED TOXICITY) **Highly Effective Methods That Are User Independent** *Failure rate of ≤1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of >1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be

consistent with local regulations regarding the use of contraceptive methods for subject in clinical studies.

b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study drug.
c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.6. Appendix 6: Definition of Bleeding Events

1. Major Bleeding in Surgical Setting[35]
   a. Fatal bleeding, and/or
   b. 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
   c. Extrasurgical site bleeding causing a fall in hemoglobin level of 20 g L-1) (1.24 mmol L-1) or more, or leading to transfusion of 2 or more units of whole blood or red cells, with temporal association within 24 to 48 hours to the bleeding, and/or
   d. Surgical site bleeding that requires a second intervention open, arthroscopic, endovascular, or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection, and/or
   e. Surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be an associate fall in hemoglobin level of at least 20 g L-1) (1.24 mmol L-1), or transfusion, indicated by the bleeding, of at least 2 units of whole blood or red cells, with temporal association within 24 hours to the bleeding.
2. Clinically Relevant Nonmajor Bleeding[28]

A modified version of clinically relevant nonmajor bleeding criteria used in the ADVANCE-2 study, in tandem with clinical judgement, will be used to classify bleeding events:

- Acute clinically overt bleeding
  - Does not satisfy additional criteria required for the bleeding event to be defined as a major bleeding event and is still considered clinically relevant. Examples are listed below:
    - Epistaxis (nose bleed):
      - Subject seeks medical attention from a physician
      - Subject visits an emergency room
      - Bleeding requires an intervention (eg, nasal pack)
      - Single bleeding episode persists for 5 minutes or more
    - Gastrointestinal bleed:
      - Vomit containing frank blood or coffee-ground material, which tests positive for blood
      - Endoscopically confirmed bleeding
      - Frank blood per rectum or melenic stools
    - Hematuria:
      - Overt, spontaneous bleeding

- Bleeding (bloody urine) persists for 24 hours or more after instrumentation

- Bruising/ecchymosis:
  - Any bruise that is assessed as "unusual" (eg, greater than expected following surgery)
- Hemoptysis:
  - Expectoration of blood or blood-stained sputum
- Hematoma:
  - Overt blood collection with the surgical wound
  - Presence of a hematoma is demonstrated radiographically (eg, ultrasound, computed tomography, magnetic resonance imaging)

Note: Any overt bleeding not meeting major or clinically relevant nonmajor criteria will be assessed[27] as minimal bleeding.

10.7. Appendix 7: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

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INVESTIGATOR AGREEMENT

JNJ-70033093

Clinical Protocol 70033093THR2001 Amendment 1

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

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Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

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_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): John Strony, MD

Institution: Janssen Research & Development

Signature: _____ Date: 11 Sep 2019

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Approved, Date: 10 September 2019

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	10-Sep-2019
Amendment JPN-1	24-July-2019
Original Protocol	11-Dec-2018

Amendment 1 (10 September 2019)

Overall Rationale for the Amendment: The overall reasons for the amendment are to modify the study design with regards to the planned and optional doses and to remove the option for preoperative dosing.

Section Number and Name	Description of Change	Brief Rationale
Title Page	The study name "**AXIOMATIC-TKR - A**ntithrombotic treatment with factor **XI**a inhibition to **O**ptimize **M**anagement of **A**cute **T**hromboembol**ic** events in **TKR**" was added to the title page.	The title page was revised to include the study name for better readability.
1.1. Synopsis Objectives and Endpoints; 3. Objectives and Endpoints	Parenthesis placement was moved in the primary objective to include all deaths in the definition of total venous thromboembolism (VTE).	Editorial error in the primary objective did not align with efficacy evaluations in the assessment of study outcomes.
1.1. Synopsis Objectives and Endpoints; 1.1. Synopsis Hypothesis; 3. Objectives and Endpoints	The hypothesis and the primary endpoint were revised to specify that the event rate will be analyzed by the "combined twice daily (BID) dose group" instead of the "combined dose group". Also, the secondary endpoint was modified in regard to the bleeding criteria because there is no International Society on Thrombosis and Hemostasis (ISTH) assessment for clinically relevant nonmajor bleeding in the surgical setting.	The language pertaining to the hypothesis, primary and secondary endpoints modified for enhanced clarity.
1.1. Synopsis Overall Design; 4.1. Overall Design; 8.2. Safety Assessments; 9. Statistical Considerations; 10.3. Appendix 3, Regulatory, Ethical, and Study Oversight Considerations, Committees Structure/Operations Committee	Text specifying the frequency of reviews of unblinded data by the Operations Committee (OC) was changed from approximately every 4 to 8 weeks to 3 to 8 weeks.	The frequency of reviews of unblinded data was modified as agreed upon with the OC.
1.1. Synopsis, Overall Design; 1.2. Schema; 4.1. Overall Design; 9. Statistical Considerations; 9.4. Periodic and Interim	The number of subjects to be included at the first interim analysis was changed from 400 to approximately 300 subjects (approximately 50 subjects in each of the JNJ-70033093 BID treatment groups). In addition, the text noting that the timing and	The number of dose groups at the onset of the study was reduced by 2 groups, therefore, the timing of the first interim analysis was changed. Because this is the first small-

Section Number and Name	Description of Change	Brief Rationale
Analyses	the cohorts will be defined in the OC charter was removed.	molecule that inhibits the activated form of human coagulation Factor XIa, flexibility was needed in determining the timing of the interim analyses during OC review of the data.
1.1. Synopsis; 1.2. Schema; 4.1. Overall Design; 6.1. Study Drugs Administered	The option to administer preoperative doses of JNJ-70033093 was removed throughout the protocol.	Academic leadership advised that preoperative dosing would not be adopted by the orthopedic community in clinical practice, therefore testing was removed from the protocol.
1.1. Synopsis; 1.2. Schema; 6.1. Study Drugs Administered; 6.3. Measures to Minimize Bias: Randomization and Blinding; 9. Statistical Considerations	• Once daily dose regimens of JNJ-70033093 were moved from the start of the study to possible doses after the interim analysis and the doses were changed from 25 mg once daily and 200 mg once daily to 50 mg once daily and 200 mg once daily. • Initial randomization changed from 1:1:1:1: 1:1:2 to 1:1:1:1:2 • Initial number of dose groups changed from 7 to 5 • Removed text noting the number of ongoing doses of JNJ-70033093 is expected to be no fewer than 4 doses.	The once daily doses were re-evaluated, and the 50 mg once daily dose will be evaluated because it more closely parallels the 25 mg BID dose and will allow for a more meaningful comparison between the once daily and BID doses.
1.1. Synopsis, Number of Subjects; 1.2. Schema; 4.1. Overall Design; 9. Statistical Considerations	Target and maximum number of subjects was changed from 1,200 and 1,500 to 900 and 1,200, respectively. Text revised to specify that this is based on the possible addition of once daily doses and/or the evaluability rate. It was also clarified that the number of subjects who were planned to be randomized into the dropped dosing regimen can be allocated to one of the other dosing groups.	The target number of subjects was changed based on the change in the study design.
1.1. Synopsis; 1.3. Schedule of Activities (SoA); 4.1. Overall Design; 4.2. Scientific Rationale for Study Design; 6.1. Study Drug Administered	• Regarding the first dose of study drug, the specification for “the day after total knee replacement (TKR) surgery” was changed to “after the end of TKR surgery” and “next day” was removed. • “PO” was removed in front of days of the visit • 10- to 14- postoperative days was changed to 10 to 14 days. • Postoperative Day 10-14 visit was changed to Day 10-14. • Footnote “r” added to SoA to specify optional pharmacodynamic (PD) samples for subjects randomized to enoxaparin.	During initiation of the study it was determined that standard-of-care in certain regions should initiate anticoagulation on the day of surgery, not the morning after surgery. Collection of the PD sample was made optional for enoxaparin subjects in order to make dosing on the evening of surgery more practical.
1.1. Synopsis; 1.2. Schema; 6.1. Study Drug Administered/Drug	Enrollment in Group E was discontinued. Subjects randomized to this group prior to Amendment 1 will continue treatment.	Once daily study drug-dose groups revised to reflect changes in the study design and allow

Section Number and Name	Description of Change	Brief Rationale
Administration	Enrollment in Group F was suspended and made optional until the OC determines that enrollment is appropriate. For Group G, the 50 mg once daily dose was added (2 capsules JNJ-70033093: 25 mg in the morning and 2 placebo capsules in the evening). Text noting that enrollment in Group G will become optional per Amendment 1 was also added. Optional Group H removed. Text noting that no optional dose will exceed a 400-mg total daily dose was removed.	flexibility of optional dosing in Groups F and G until final determination by the OC.
1.1. Synopsis, Study Drug Groups and Duration; 1.3. Schedule of Activities (SoA), Footnote 1; 4.1. Overall Design; 6.1. Study Drug Administered; 6.5. Concomitant Therapy	Text added specifying that the study drug "must be the first anticoagulant administered postoperatively".	Text was needed to clarify the timing of postoperative doses of other anticoagulants in relation to the study drug.
1.1. Synopsis, Safety Evaluations; 1.1. Synopsis, Statistical Methods; 1.3. Schedule of Activities (SoA), Footnote t; 4.1. Overall Design; 8.2. Safety Assessments; 8.3.1. Adverse Events of Interest; 8.3.1.3. Liver Enzyme Elevations and Clinical Liver Events; 9.3.2. Safety Analyses	Changed terminology of Adverse Events of Special Interest to "Adverse Events of Interest".	Terminology changed because for this study expected events and study endpoints are considered adverse events of interest.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis Endpoints; 1.1. Synopsis Pharmacokinetic Evaluations; 1.1. Synopsis Statistical Methods; 3. Objectives and Endpoints; 8.5.3. Pharmacokinetic Parameters and Evaluations; 9.3.3. Other Analyses	For the study endpoints as well as the pharmacokinetic evaluations, the word "level" was removed from the description of JNJ-70033093 exposure.	Exposure level is not a typical description. Therefore, the term "exposure" alone is sufficient as the exposure level is not defined in the protocol.
1.1. Synopsis, Overall Design; 4.1. Overall Design; 6.2. Preparation/ Handling/Storage/ Accountability; 6.4. Study Drug Compliance	Text added noting that selected sites may also use scanning technology to manage clinical study supplies and drug compliance activities. Subjects enrolled at selected sites may use an application on the subject's own smartphone/tablet to confirm study drug administration (JNJ-70033093 capsules only) and receive notifications as per protocol scheduled events (eg, next clinical site visit) as well as additional study information.	Adding pilot program at selected sites to compare manual methods of compliance monitoring, subject retention, end-to-end subject engagement, and drug accountability with an automated method.
1.3. Schedule of Activities (SoA)	• Timing for randomization was changed from Day of surgery -2 to postoperatively, following the primary unilateral elective TKR surgery. In addition, the statement that all subjects must be randomized prior to surgery was removed. • Laboratory samples at the up to Day -30 timepoint were removed. The Factor XI (FXI) antigen required at this time point was also moved to 0 hour. • Specified that enoxaparin may be administered preoperatively 12 hours prior to the surgical procedure in accordance with local standard-of-care. Sites that routinely administer preoperative enoxaparin should continue their standard practice for all study subjects at that site. Per standard-of-care, study drug should not be used for the preoperative dose of enoxaparin for subjects in either treatment group.	As a result of the removal of JNJ-70033093 preoperative dosing, randomization will now be conducted postoperatively because the first dose of study drug will not be administered until 12 to 24 hours after wound closure. In addition, laboratory samples to be collected prior to surgery are no longer necessary since the 0-hour samples will be collected prior to study drug for all subjects. Because randomization will now occur postoperatively, clarification added that 0-hour samples cannot be drawn until after randomization because some are conditional samples based on the treatment group.
1.3. Schedule of Activities (SoA)	Text added to footnote d: Day 4 procedures may be conducted up to +2 days (ie, samples may be drawn on Days 5 or 6) and Day 7 procedures may be conducted +2 days (ie, Day 8 or 9).	Text added to allow flexibility with laboratory testing on weekend days.
1.3. Schedule of Activities (SoA), Footnote e; 6.1. Study Drugs Administered	Text added to clarify that if using the +6-hour window to allow the 12-hour sample to be drawn the following morning, the evening dose of study drug on Day 1 or Day 4 should be administered, but there must be a minimum of 6 hours between doses on these days.	Twice daily dosing should commence at the initiation of treatment and should not be dictated by the pharmacokinetic (PK) sample schedule.
1.1. Synopsis; 1.3. Schedule of Activities (SoA), Footnote q; 6.1. Study Drug Administered	Text added to specify that on the day of the Day 10-14 visit, study drug dosing should occur first thing in the morning, and the PK sample should not be drawn until at least	Text added for clarity on handling of PK samples and dosing.

Section Number and Name	Description of Change	Brief Rationale
	1 hour after the dose is taken. Also added text noting that subjects who discontinue study drug early do not need to have PK sampling conducted at any subsequent visits.	
2.2. Background	Table 1 updated.	Changes reflect the most recent edition of the Investigator's Brochure, Edition 5.
4.1. Overall Design	Modified text to specify the OC may unblind any member of the Steering Committee and that any member unblinded will no longer be involved in the operational aspects of the trial.	Revised to allow the OC flexibility in consulting with the Steering Committee members when discussing data resulting in recommendations to revise the study design.
4.1. Overall Design	Deleted sentence: Pharmacokinetic, PD, and biomarker samples will also be collected and assessed.	Corrected error, since PK/PD samples will not be collected at Week 6.
4.2. Scientific Rationale for Study Design, Choice of Comparator	Clarified text to add that 40-mg daily dose of enoxaparin will be used in this study as it is the dosage regimen used in "most" approved countries for the indication being studied.	Text modified because some countries use enoxaparin 30 mg or 20 mg BID for VTE prophylaxis post TKR surgery.
4.2. Scientific Rationale for Study Design, Choice of Biomarkers	Text changed from postoperatively "at approximately 12 to 24 hours" to "on Day 1 (0 hour) prior to study drug administration".	Text edited to reflect the correct time the cardiac troponins would be drawn postoperatively.
4.3. Justification for Dose	Additional justification provided for using a more conservative approach for the lowest proposed once daily dose based on maintaining pharmacological effect of aPTT prolongation at ≥1.5 times over the full dosing interval.	Additional language needed to justify the lowest proposed once daily dose.
5.1. Inclusion Criteria; 5.3. Lifestyle Considerations	Half-life restrictions for birth control measures were increased by 2 days. The following criteria were updated accordingly: • #8 Requirement for birth control for females was increased from 32 to 34 days • #9 Requirement for egg donation for females was increased from 32 to 34 days • #10 Requirement for birth control for males was increased from 92 to 94 days • #11 Requirement for sperm donation for males was increased from 92 to 94 days	Updated to take a more conservative approach by utilizing the upper end of the JNJ-70033093 half-life for birth control measures. The half-life of JNJ-70033093 as 18 hours versus 11 hours was used and therefore, the 5 half-lives of the study drug increased to 4 days rather than the 2 days previously used.
5.2. Exclusion Criteria	Second bullet from Exclusion Criterion 4 was removed. Exclusion Criterion 5 corrected to state contrast-induced nephropathy instead of neuropathy Exclusion Criterion 8 modified to include sensitivities to heparin and pork products	Exclusion criteria revised for clarity.
5.3. Lifestyle Considerations	The following criterion was modified: #3 Timepoint requirement for the restriction on donating blood was changed from "at least	Lifestyle restriction revised for clarity.

Section Number and Name	Description of Change	Brief Rationale
	4 days after completion of the study" to "until after completion of the study"	
5.4. Screen Failures	Text noting subjects eligible for rescreening only in cases when TKR surgery is rescheduled outside of the 30-day window was removed.	Text was deleted to allow subjects to be rescreened for reasons other than rescheduled surgery.
6.1. Study Drug Administered, Drug Administration	Language added to specify that if a dose of JNJ-70033093 is missed, the capsule should be taken as soon as possible; 2 doses can also be taken together in the evening if the morning dose is missed. No more than 2 doses should be taken in 1 day.	Instructions added to give direction for what to do for a missed dose of JNJ-70033093 study drug.
6.2. Preparation/Handling/ Storage/Accountability	Temperature range for storage of study drug was removed and text was added noting the storage conditions would be specified in the product label.	Text removed for consistency with the product label.
6.5. Concomitant Therapy	Removed text specifying that "in those situations where the study drugs are administered preoperatively, intermittent pneumatic compression is still permitted until the time of the first postoperative dose of the study drug".	Text removed, given that the option for preoperative dosing was removed.
7.2. Subject Discontinuation/Withdrawal From the Study	The last sentence in this section was revised to state that if a subject discontinues study drug and does not withdraw consent, then the subject should continue to have all remaining assessments completed.	Language modified because continuation of remaining study procedures should not be applicable to subjects who withdraw consent.
8. Study Assessments	Blood volume in the table for high-sensitive cardiac troponin T (hs-cTnT) sample is 4.0 mL not 2.7 mL, and the total blood volume was changed from 155.7 to 134.9 mL. Total blood volume collected in the study noted in the table also was corrected (approximately 135 mL, with 95 mL for PD/biomarkers). Total blood volume for subjects randomized to enoxaparin was also added (115 mL) to the text because no PK samples are drawn.	Corrected discrepancy in the volume of laboratory samples between volume of blood to be collected for each subject and the actual volumes of the collection tubes that are supplied by the central laboratory.
8. Study Assessments; 8.2.4. Clinical Safety Laboratory Assessments	The timepoint for collection of the hematology and chemistry laboratory tests and urine sample for urinalysis at screening was removed.	Text revised to align with the sequence of laboratory assessments specified by the central laboratory. In addition, timepoints of hematology and chemistry laboratory tests and urine sample were modified. Screening laboratory testing was removed because preoperative dosing will not be implemented.
8.3.1.3. Liver Enzyme Elevations and Clinical Liver Events	Modified language to clarify the criterion of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥3 times (x) upper limit of normal (ULN), confirmed by repeat is not required to be reported as an adverse event of interest.	Expected reporting of liver enzyme elevations as adverse events of interest clarified. Previous language was unclear, the liver enzyme elevations do not meet the criteria for

Section Number and Name	Description of Change	Brief Rationale
		mandatory adverse event of interest reporting.
8.3.6. Pregnancy	Text edited to note that if a subject becomes pregnant during the study, the subject must be discontinued from further study intervention.	Pregnancy is an exclusion criterion for the study, therefore study drug should be discontinued in the event of pregnancy.
8.4. Treatment of Overdose	Text edited to specify the threshold for reporting an overdose applied to both JNJ-70033093 and enoxaparin and overdose that is considered excessive and medically important by the investigator should be reported as a serious adverse event (medically important event).	Corrected language to include enoxaparin because the protocol text defined the threshold for reporting an overdose of JNJ-70033093 but not enoxaparin.
8.5. Pharmacokinetics	Pharmacokinetic specimen type changed from serum samples to plasma samples.	Correction that PK samples are plasma samples. Typo, wording contains incorrect PK specimen type.
9.1. Sample Size Determination, Table 2	Assumed total VTE rate for 25 mg once daily was deleted and the assumed rate of 24% was added for 50 mg once daily.	Table was updated to reflect the change in planned once daily dosing because it is anticipated that 50 mg once daily, as the lowest once daily dose being tested, would perform at a level equivalent to enoxaparin.
9.2. Populations for Analyses	Week 6 visit was removed from the description of the modified intent-to-treat (mITT) population.	The description for the mITT population revised because subjects will have only 1 valid venography visit at Day 10-14.
9.3.1. Efficacy Analyses	The study objective was modified to add text noting the importance of showing a statistically significant <30% event rate in total VTE in the combined dose group. The text noting that data from preoperative dose regimens will not be used in the modified MCP-Mod analysis and separate analysis was deleted.	The statistical rationale for the study objective was revised for clarity.
9.3.2. Safety Analyses	Edited text to specify that height and weight will be summarized.	Changes in physical examination are not specified in the electronic case report form (eCRF). Any changes in physical examination are evaluated and captured as adverse events as appropriate. Height and weight are recorded in the eCRF.
10.6. Appendix 6/ Definition of Bleeding Events	The description of clinically relevant nonmajor bleeding was revised to indicate a modified version of the criteria from the ADVANCE-2 study, in tandem with clinical judgement, will be used to classify clinically relevant nonmajor bleeding events.	Modified to be in alignment with the standard practice used by the Clinical Events Committee (CEC).

Section Number and Name	Description of Change	Brief Rationale
	Also, the descriptions listed for each bleeding type are examples not criteria. The example of a hematoma was revised to remove “and a drop of hemoglobin is present with no external evidence of bleeding”. The description of minimal bleeding was revised to specify it specifically must be considered a “clinically overt” bleeding event to be included in this category. Moved reference 27, Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. N Engl J Med. 2009;361(6):594-604, from the clinically relevant nonmajor category to the minimal bleeding definition.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

PROTOCOL AMENDMENTS

Protocol Version	Date
Original Protocol	11 December 2018
Amendment JPN-1	24 July 2019

Amendments below are listed beginning with the most recent amendment.

Amendment JPN-1 (24 July 2019)

The overall reason for the amendment: The overall reason for the amendment is to modify inclusion criterion and add exclusion criterion at the request of the Japanese Health Authorities (Pharmaceuticals and Medical Devices Agency [PMDA]).

Applicable Section(s)	Description of Change(s)
Rationale: Inclusion Criteria revised to include detail and further clarification.	
Section 5.1 Inclusion Criteria	Added blood pressure as an example of vital signs measurements in inclusion criterion #3. Added hemoglobin, platelet, PT and aPTT as examples of clinical laboratory tests performed in inclusion criterion #4.
Rationale: To exclude subjects at high risk of bleeding and with a known history of stroke as outlined in Exclusion Criteria #19 and #20.	
Section 5.2 Exclusion Criteria	Added new exclusion criterion #19, “Subjects at a high risk of bleeding, including subjects who would require a reduction of LMWH (eg, reduced creatinine clearance), elderly patients and/or low body weight patients”. Added new exclusion criterion #20, “Subjects with underlying diseases or medical history of the cerebrovascular system, such as medical history of stroke”.
Rationale: Minor edits made for clarity.	
Throughout the protocol	Minor, consistency and logical clarifications were made throughout the document, which do not affect the overall study concept.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1/JPN-1	19-Sep-2019
Amendment 1	10-Sep-2019
Amendment JPN-1	24-July-2019
Original Protocol	11-Dec-2018

Amendment 1/JPN-1 (19 September 2019)

Overall Rationale for the Amendment: The overall reason for the amendment is to make Japan specific changes (ie, modify inclusion criterion and add exclusion criterion) to the Global Protocol Amendment 1 at the request of the Japanese Health Authorities (Pharmaceuticals and Medical Devices Agency [PMDA]).

Section Number and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria	Added blood pressure as an example of vital signs measurements in Inclusion Criterion #3. Added hemoglobin, platelet, PT and aPTT as examples of clinical laboratory tests performed in Inclusion Criterion #4.	Inclusion Criteria revised to include detail and further clarification.
5.2. Exclusion Criteria	Added new Exclusion Criterion #19, “Subjects at a high risk of bleeding, including subjects who would require a reduction of LMWH (eg, reduced creatinine clearance), elderly patients and/or low body weight patients”. Added new Exclusion Criterion #20, “Subjects with underlying diseases or medical history of the cerebrovascular system, such as medical history of stroke”.	To exclude subjects at a high risk of bleeding and with a known history of stroke as outlined in Exclusion Criteria #19 and #20.

Janssen Research & Development

Statistical Analysis Plan

A Randomized, Open-Label, Study Drug-Dose Blind, Multicenter Study to Evaluate the Efficacy and Safety of JNJ-70033093 (BMS-986177), an Oral Factor XIa Inhibitor, Versus Subcutaneous Enoxaparin in Subjects Undergoing Elective Total Knee Replacement Surgery

Protocol 70033093THR2001; Phase II

JNJ-70033093

Status: Approved

Date: 26 September 2019

Prepared by: Janssen Research & Development, LLC

Document No.: EDMS-ERI-197223295, 1.0

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

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LIST OF IN-TEXT FIGURES

ABBREVIATIONS

AE	adverse event
ALT/SGPT	alanine aminotransferase
APAC	Asia Pacific
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic class
BID	twice daily
BMI	body mass index
CEC	Clinical events committee
CI	confidence interval
CRF	case report form
CRNM	clinically relevant non-major
CSR	Clinical Study Report
CV	coefficient of variation
DPS	Data Presentation Specifications
DVT	Deep vein thrombosis
(e)CRF	(electronic) case report form
FAS	full analysis set
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IQ	interquartile
IWRS	interactive web response system
LATAM	Latin America
MCP-Mod	multiple comparison procedures and modeling
MedDRA	Medical Dictionary for Regulatory Activities
MINS	Myocardial injury in noncardiac surgery
(m)ITT	(Modified) intent-to-treat
N	Total number
NA	North America
OC	Operations committee
PD	Pharmacodynamic
PE	pulmonary embolism
PI	principal investigator
PK	pharmacokinetic(s)
PP	per protocol
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SDS	Secure Data Supplier
SMQs	standardized MedDRA queries
TEAE	treatment-emergent adverse event
TKR	Total knee replacement
VTE	Venous thromboembolism
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) specifies definitions of analysis sets, key derived variables, and statistical methods for analysis of efficacy and safety for the Phase 2 study 70033093THR2001. This SAP is based on the Clinical Protocol 70033093THR2001 amendment 1 dated September 10, 2019. Titles, mock-ups and programming instructions for all statistical outputs (tables, figures and listings) will be provided in a separate document entitled Data Presentation Specifications (DPS). This SAP and its associated DPS will be used to generate a topline report and a Clinical Study Report (CSR) after database lock.

1.1. Trial Objectives

Primary Objective

- To determine the efficacy of JNJ-70033093 in preventing total VTE events (proximal and/or distal DVT [asymptomatic confirmed by venography assessment or objectively confirmed symptomatic], nonfatal PE, or any death) during the treatment period

Secondary Objectives

- To assess the dose-response of JNJ-70033093 for the occurrence of the endpoint of any bleeding events during the treatment period
- To determine the efficacy of JNJ-70033093 in preventing total VTE events during the full study period
- To assess the dose-response of JNJ-70033093 for the rate of any bleeding throughout the full study period
- To assess the dose-response of JNJ-70033093 for the prevention of major VTE (death, asymptomatic or symptomatic proximal DVT or nonfatal PE) during the treatment period and throughout the full study period
- To assess the effect of individual doses of JNJ-70033093 compared with enoxaparin for both efficacy and safety endpoints
- To compare the effect of JNJ-70033093 with enoxaparin for the individual components of the total VTE endpoint
- To assess the PK of JNJ-70033093 in men and women undergoing primary unilateral TKR surgery and the relation of these measures to efficacy and safety endpoints (e.g., exposure-response analyses)

Exploratory Objectives

- To evaluate PD to assess its relationships to PK and the relation of these measures to efficacy and safety endpoints (e.g., exposure-response analyses).
- To evaluate exploratory biomarkers to assess their relationship to the probability of total VTE during the treatment period.
- To explore the presence and incidence of asymptomatic myocardial injury in noncardiac surgery (MINS) as it relates to total knee arthroplasty.

The full study period and the treatment period are defined in Section 2.3.

1.2. Trial Design

This is an open-label, study drug-dose blind, active-controlled, multicenter, dose-ranging study of JNJ-70033093 in subjects undergoing primary unilateral elective TKR surgery. The study uses the prospective, randomized, open-label, blinded endpoint (PROBE) design. Men and women who are ≥50 years of age are eligible to participate if they are considered medically stable and appropriate for anticoagulant prophylaxis as determined by the investigator and on the basis of clinical laboratory tests performed as part of screening for elective TKR surgery. A target of 900 subjects will be randomly assigned to treatment in this study, with an option to increase the randomization target to approximately 1,200 subjects based on the possible addition of QD dose groups, and/or evaluability rate.

Subjects meeting all of the enrollment criteria will be eligible to enter the study. The study will be conducted in 3 phases, which includes an up to 30-day screening phase before surgery, a 10- to 14-day postoperative dosing phase, and a 4-week ±10 days follow-up phase. Unscheduled visits may be performed at the discretion of the investigator for the assessment of any potential bleeding or efficacy endpoint events. The total duration of participation following randomization will be approximately 6 weeks.

Screening for eligible subjects will be performed within and including 30 days before administration of the first dose of postoperative study drug. Eligible subjects will be randomly assigned to treatment with either JNJ-70033093 or enoxaparin postoperatively following unilateral elective TKR surgery. Subjects will know the treatment to which they were assigned but subjects randomly assigned to JNJ-70033093 will remain blinded to the dose and frequency (i.e., BID versus QD).

First dosing of both study drugs will occur while the subject is still hospitalized, with administration beginning a minimum of 12 hours and a maximum of 24 hours after the end of TKR surgery, which is defined as the time of wound closure, and must be the first anticoagulant administered postoperatively.

Enoxaparin may be initiated preoperatively at least 12 hours prior to the surgical procedure in accordance with local standard-of-care. Sites that routinely administer preoperative enoxaparin should continue their standard practice for all study subjects at that site. Per standard-of-care, study drug should not be used for the preoperative dose of enoxaparin for subjects in either treatment group.

Following discharge or transfer to an alternate facility, subjects will continue to take the assigned study drug for a total of 10 to 14 days. Unilateral venography assessment of the operated leg will be performed within 1 calendar day after the last dose of either JNJ-70033093 or enoxaparin is taken.

Subjects will return to the study site 6 weeks after the TKR surgery for study-related evaluations and procedures as described in the Schedule of Activities. Safety evaluations will include the monitoring of all adverse events (AE), including nonserious adverse events, serious adverse events (SAE), adverse events of interest (i.e., bleeding events, liver enzyme elevations and

clinical liver events, wound or joint complications), clinical laboratory tests (i.e., hematology, clinical chemistry, urinalysis), and physical examinations.

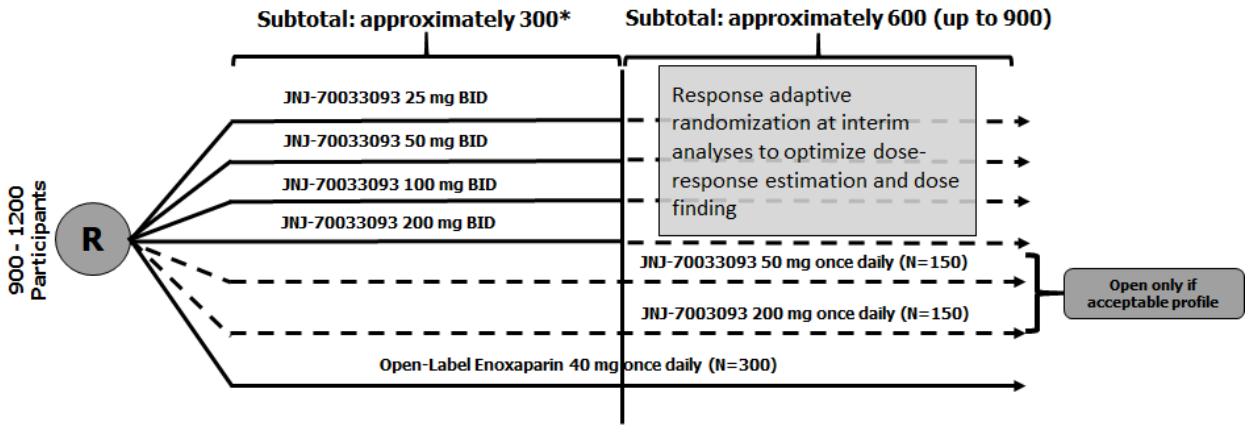
An Operations Committee (OC), Steering Committee, and independent Clinical Events Committee (CEC) will be commissioned for this study. The OC will be unblinded and the Steering Committee will be blinded to the dose and frequency of JNJ-70033093, unless the OC finds it necessary to consult with and unblind select members of the Steering Committee. If any members of the Steering Committee are unblinded to the dose and frequency of JNJ-70033093, they will no longer be involved in the operational conduct of the study. The CEC will be blinded to both the study drug and the dose. The OC will be responsible for reviewing ongoing safety and efficacy data by unblinded subject treatment assignments approximately every 3 to 8 weeks on a periodic basis.

Unblinded periodic and interim analyses will be conducted by the OC for the purposes of safety oversight and as part of the adaptive approach. The first interim analysis will be triggered when approximately 300 subjects (approximately 50 subjects in each of the JNJ-70033093 BID treatment groups) will have completed venography or have had a symptomatic VTE event. Both periodic and the interim analyses results will be used to guide the decision to drop a dose of JNJ-70033093 and/or readjust the randomization ratio. The number of subjects who were planned to be randomized into the dropped dosing regimen can be allocated to one of the other dosing groups. The interim analysis will also serve as the formal venue to assess study status and possibly add once-daily dosing of JNJ-70033093 based on available efficacy and safety data. If PK/PD analysis results are available at the time of the interim analysis, the results will be included in the review.

Additional interim analyses will be conducted, as needed, at the discretion of the OC.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



Study drug-dose blind design: Treatment with enoxaparin or JNJ-70033093 will be open-label but blinded to study drug dose and regimen for all subjects randomized to JNJ-70033093. All subjects will receive study drug for 10 to 14 days of randomized treatment, followed by unilateral venography and a follow-up study visit at Week 6.

* Interim Analysis to be conducted when approximately 50 subjects in each of the BID treatment groups subjects have completed the venography or have had a symptomatic VTE event.

** Additional interim analyses will be conducted, as needed, at the discretion of the Operations Committee (OC). These decisions will be made only after taking the safety and efficacy profiles of JNJ-70033093 into account.

1.3. Statistical Hypotheses for Trial Objectives

The study objectives include proof-of-efficacy and estimation of dose-response relationship in total VTE. This objective can be achieved either by showing a statistically significant dose-response trend (i.e., the alternative hypothesis is that there exists monotone dose-response trend), or by showing a statistically lower total VTE event rate in combined BID data compared with 30% (i.e., the alternative hypothesis is that the event rate of combined BID dose is less than 30%). The rate of 30% is a conservative estimate of the total VTE rate in subjects given placebo. The trend test consists of contrast tests defined by prespecified candidate models (4 E_{max} dose-response modules with varying degrees of ED_{50}, Figure 2), which provide estimates of dose-response (taking BID and once daily into consideration).

1.4. Sample Size Justification

A target of 900 subjects will be randomly assigned to treatment in this study, with an option to increase the randomization target to approximately 1,200 subjects based on interim analysis results and/or evaluability rate.

Assuming the evaluability rate (rate of subjects with a valid assessment of potential efficacy outcome and who take at least 1 dose of study drug) is 80%, if the true underlying total VTE event rates are as shown in Table 1, the study is expected to have over 99% power to declare proof-of-efficacy at 1-sided 5% significance level. Proof-of-efficacy is defined as either a statistically significant dose-response trend or primary endpoint event rate for the combined BID JNJ-70033093 groups that is statistically lower than 30%. The exact power will vary because of the nature of the adaptive study design.

The highest dose of JNJ-70033093 with acceptable safety will be compared against enoxaparin. For example, if the highest dose for acceptable safety is 200 mg BID, the number of evaluable subjects at this dose and enoxaparin groups is expected to be 120 and 240 subjects respectively, the power to detect a statistically significantly lower total VTE event rate against enoxaparin, at 1-sided 5% significance level, is over 90%.

Table 1: Assumed Total VTE Event Rates by Treatment Group in Sample Size Determination

	JNJ-70033093				Enoxaparin 40mg once daily
	25 mg	50 mg	100 mg	200 mg	
BID	18%	14.5%	12.5%	11.0%	
Once daily		24%		14%	23.8%

BID = twice daily, VTE = venous thromboembolism

1.5. Randomization and Blinding

Randomization

Initially, subjects will be assigned in a 1:1:1:1:2 ratio into 1 of 5 treatment groups, including 4 dose regimens of JNJ-70033093 and enoxaparin 40 mg once daily based on an algorithm implemented in the interactive web response system (IWRS). Following the decision of altering randomization scheme by dropping and/or adding treatment arms, and/or changing randomization ratio, the IWRS will be updated for randomization accordingly. Subjects will be stratified by region using dynamic central randomization to minimize the imbalance in the distribution of the number of subjects across study drug groups. Based on the algorithm, the IWRS will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the dosing blind for an individual subject. More details of blinding in the subject level could be found in Section 6.3 of the protocol amendment 1.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. If a subject has 2 or more actual visits in one scheduled visit, the earliest visit will be used as the protocol visit for that analysis visit. This is mainly for the lab test analyses for the changes from baseline.

2.2. Pooling Algorithm

Not applicable.

2.3. Analysis Sets

Each analysis involves the following two aspects:

- The analysis set, which specifies those subjects who will be included in an analysis.
- The observation (or analysis) period, which specifies the time window within which data will be included in an analysis.

The following analysis sets: All Randomized Analysis Set, Intent-to-treat Analysis set (ITT), Safety Analysis Set, modified Intent-To-Treat Analysis Set (mITT), Per Protocol (PP) Analysis Set, and PK/PD Analysis Sets, will be used.

Associated with the analysis sets, three Analysis periods are defined as follows.

- Day 14: this period is defined as from Day 1 to Day 17 (inclusive).
- Week 6: this period is defined as from Day 1 to the last contact date.
- On-treatment: this period is defined as from Day 1 to last dose date + 2 days.

Day 1 refers to date of the first dose of study drug administration or the surgery date if the subject didn't take any study drug (see Section 2.5); Day 14 period and On-treatment period refer to the treatment period in different scenarios; Week 6 period refers to the full study period.

2.3.1. All Randomized Analysis Set

The all randomized analysis set includes all subjects who were randomized in the study regardless of whether they took study drug.

2.3.2. Intent-to-treat Analysis Set

The Intent-to-treat (ITT) (as termed Full Analysis Set [FAS] in the International Conference on Harmonization [ICH] E9 guideline) analysis set includes all randomized subjects who have signed an informed consent form.

2.3.3. Efficacy Analysis Sets

2.3.3.1. Primary Efficacy Analysis Set

The modified Intent-to-treat (mITT) analysis set includes all ITT subjects who received at least 1 dose of study drug with an evaluable venography assessment or a confirmed symptomatic VTE event or any death as adjudicated by CEC. This will be identified as mITT (CEC).

Evaluable venography assessment at Day 14 is defined as the venography assessment with an evaluable result of the leg between Day 8 and Day 17. Subjects with unevaluable venography result as deemed by the CEC will be excluded from the primary efficacy analysis set mITT (CEC).

Primary efficacy analysis is based on the mITT analysis set associated with Day 14 analysis period.

In addition, the following distinctions will be implemented in data summary outputs whenever needed.

- Modified intent-to-treat analysis set (mITT) (Investigator) will be associated with investigator reported results.
- Modified intent-to-treat analysis set (mITT) (Best available) will be associated with the best available results, where best available event is defined as follows:
    - If an event is CEC adjudicated, then best available event is the CEC adjudicated event.
    - Otherwise, if an event is not CEC adjudicated, then best available event is the investigator reported event.

The mITT (Best available) analysis set will only be applicable to the interim analyses and the planned periodic reviews. At the time of database lock at the end of the study, all CEC adjudication of events will be completed. Hence, after the database lock, the mITT (Best available) analysis set will be identical to the mITT (CEC) analysis set.

2.3.3.2. Secondary Efficacy Analysis Sets

The mITT analysis set at Week 6 is defined as the mITT analysis set at Day 14 plus the subjects who had no evaluable venography results at Day 14 visit but had symptomatic events or had evaluable venography results after Day 14 visit. The efficacy analysis based on this analysis set is associated with the Week 6 analysis period.

Per Protocol (PP) analysis set includes all mITT subjects with no key protocol deviations. Key protocol deviations are defined as follows,

- Developed withdrawal criteria but not withdrawn
- Randomized but did not satisfy key criteria
- Received a disallowed concomitant treatment
- Received study drug which is different from the treatment group randomized by the IWRS or an incorrect dose of study drug
- Was randomized but did not receive study drug

Key criteria are specified in the major protocol deviation document (TV-FRM-04718).

2.3.4. Safety Analysis Set

The safety analysis set includes all ITT subjects who received at least 1 dose (partial or complete) of study drug.

2.3.5. Pharmacokinetics Analysis Set

The PK analysis set consists of subjects who have received at least 1 dose of JNJ-70033093 and have at least one valid blood sample drawn for PK analysis.

2.3.6. Pharmacodynamics Analysis Set

The PD analysis set is defined as subjects who have received at least 1 dose of study drug and at least one valid blood sample drawn for PD analysis.

2.4. Definition of Subgroups

The following subgroups (see Table 2) will be used to summarize the total VTE efficacy and any bleeding event data.

Table 2: Definition of Subgroups

Subgroup	Variant Definition
Region	• Western Europe (Belgium, Greece, Israel, Italy, Portugal, South Africa, Spain) • Eastern Europe (Bulgaria, Hungary, Lithuania, Latvia, Poland, Russia, Turkey, Ukraine) • APAC (Asia Pacific: Australia, Japan, Malaysia, Thailand) • LATAM (Latin America: Argentina, Brazil, Mexico) • NA (North America: Canada and USA)
Age Group	• 50 - <65 years • 65 - <75 years • ≥75 years
Sex	• Female • Male
Race	• White • Asian • African American • Others
BMI	• underweight <18.5 kg/m^2 • normal 18.5-<25 kg/m^2 • overweight 25-<30 kg/m^2 • obese ≥30 kg/m^2
D-Dimer	• ≥ 2X ULN* • < 2X ULN*
Renal function (Creatinine Clearance Level)	• 30-<50 ml/min • 50-<80 ml/min • ≥ 80 ml/min
Surgery duration	• < 2 hours • ≥ 2 hours
Tourniquet use	• Yes • No
Aspirin/nonsteroidal anti-inflammatory drugs at baseline	• Yes • No

*ULN = upper limit of normal

2.5. Study Day and Relative Day

Day 1 refers to the date of the first dose of study drug administration or the surgery date if the subject didn't take any study drug. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - date of Day 1 + 1, if visit date ≥ date of Day 1
- Visit date - date of Day 1, if visit date < date of Day 1.

There is no 'Day 0'.

The last contact date is defined as the maximum of the following dates,

- Dates of all study-related visits (including scheduled or unscheduled visits);
- Dates of all study-related procedures, findings and events, including, but not limited to AE, concomitant medications, disposition, clinical laboratories, and death.

2.6. Baseline and Endpoint

Baseline is defined as the last observation prior to the first dose of study drug or the surgery if no study drug is taken.

Endpoint is defined as the available postbaseline result within the analysis period. Unscheduled visit results are included in this definition.

2.7. Imputation Rules for Missing Date/Time

Partial (missing) first dose (postoperative) date will be imputed as follows:

- If the partial date is missing day only, it will be set to:
    - First day of the month of the partial date, if month/year of the partial date is different than the month/year of the surgery day;
    - The surgery day if the month/year of the partial date is the same as the month/year of the surgery day.
- If the partial date is missing both day and month, it will be set to:
    - January 1 of the year of the partial date, if the year of this date is after the year of the surgery day;
    - The surgery day, if the partial date is the same year of the surgery day.

Completely missing first dose (postoperative) dates will not be imputed for the safety population.

Partial last dose date will be imputed as follows:

- If the partial last dose date is missing day only, it will be set to the earliest of
    - the last day of the month of the partial last dose date;
    - the surgery day + 14 days;
    - the evaluable venography day.
- If the partial last dose date is missing both day and month, it will be set to the earliest of
    - December 31 of the year of the partial last dose date;

  - the surgery day + 14 days;
  - the evaluable venography day.
- Completely missing last dose dates will not be imputed for the safety population.

Partial AE onset dates will be imputed as follows:

- If the onset date of an AE is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the first dose date;
  - The first dose date, if the month/year of the onset of AE is the same as month/year of the first dose date and month/year of the AE resolution date is different;
  - The first dose date or the day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the first dose date and month/year of the AE resolution date are same;
- If the onset date of an AE is missing both day and month, it will be set to, but no later than the AE resolution date:
  - January 1 of the year of onset date, as long as this date is on or after the first dose date;
  - Month and day of the first dose date, if this date is the same year that the AE occurred;
  - Last day of the year if the year of the AE onset is prior to the year of the first dose date;
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an AE is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month;
- If the resolution date of an AE is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

Missing times of AE onset/resolution dates will be imputed as follows:

- A missing time of onset of an AE will be set to the earlier of:
  - 00:01 as long as the date is after Day 1;
  - The time of the first dose or the time of surgery for untreated subjects if this is the same day of Day 1.

If a missing time is associated with a partial or missing date, the date will be imputed prior to imputing the time.

3. PERIODIC AND INTERIM ANALYSES

The OC will be responsible for reviewing ongoing safety and efficacy data by unblinded subject treatment assignments approximately 3 to 8 weeks on a periodic basis. The first interim analysis will be triggered when approximately 300 subjects (approximately 50 subjects in each of the JNJ-70033093 BID treatment groups) will have completed the venography or have had a symptomatic VTE event. Additional interim analyses will be conducted, as needed, at the discretion of the OC.

Both periodic reviews and interim analyses will require an independent Statistical Support Group (SSG). Details of the operation of the OC are provided in the OC Charter. There will be no separate OC SAP.

3.1. Interim Analyses

The unblinded interim analyses will be conducted by the OC as part of the adaptive approach that may be used to guide decisions to drop a dose of JNJ-70033093, and/or adjust the randomization ratio based on available efficacy and safety data. The objectives of the interim analyses are to:

- Test futility
- Test dose-response trends to determine if the dose range being studied is appropriate for both efficacy and safety. Note, it is not intended that the study will stop early due to statistically significant dose-response trend
- Determine if a dose should be added and/or dropped to optimize data collection for dose-response modeling
- Determine how to allocate the remaining subjects optimally based on observed efficacy, safety or balanced efficacy/safety results.

Subjects randomization will be balanced in the active dose groups until the first OC committee review. Regarding adaptation guidelines, including futility, adding/dropping a dose, modification of the randomization ratio, see Section 7 of the OC Charter.

The first interim analysis will be triggered when approximately 300 subjects (approximately 50 subjects in each of the JNJ-70033093 BID treatment groups) will have completed the venography or have had a symptomatic VTE event. Before the first interim analysis OC meeting, a data cut-off date will be identified, and data cleaning efforts will be intensified in preparation for the creation of analysis data sets. The study programming team will transfer the blinded data to the SSG, and the IWRS vendor (Bracket) will transfer the randomization code to Secure Data Supplier (SDS). The SSG will then obtain the treatment assignment dataset from the SDS prior to the interim analysis and the unblinded report will be provided to the OC.

Additional interim analyses will be conducted, as needed, at the discretion of the OC. These decisions will be made only after taking the safety and efficacy profiles of JNJ-70033093 into account.

The significance level will not be adjusted for the final analysis.

4. SUBJECT INFORMATION

The number of subjects in each analysis set will be summarized and listed by separate treatment groups, combined active treatment groups and overall group. In addition, the distribution of subjects by region, country, and site ID will be presented unless otherwise noted.

4.1. Demographics and Baseline Characteristics

Table 3 presents a list of the demographic variables and baseline characteristics that will be summarized for the ITT, mITT, PP and safety analysis sets.

Table 3: Demographic Variables and Baseline Characteristics

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (total number [N], mean, standard deviation [SD]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m2)	
Categorical Variables	
Age (50 - <65 years, 65 - <75 years and ≥ 75 years)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female)	
Race[a] (White, Asian, African American and others)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI (underweight <18.5 kg/m2, normal 18.5-<25 kg/m2, overweight 25-<30 kg/m2, obese ≥30 kg/m2)	
Renal function (CrCl[b] 30-<50 ml/min, 50-<80 ml/min, ≥ 80 ml/min)	
D-Dimer (≥ 2X ULN[c], < 2X ULN)	
Surgery duration (< 2 hours, ≥ 2 hours)	
Tourniquet use (Yes, No)	
Aspirin/nonsteroidal anti-inflammatory drugs at baseline (Yes, No)	
Reason for surgery (Osteoarthritis, Rheumatoid arthritis, Osteonecrosis and Other)	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'
[b] CrCl = creatinine clearance. [c]ULN = upper limit of normal

4.2. Disposition Information

Screened subjects and reason for screen failures will be summarized.

The number of subjects in the following disposition categories will be summarized throughout the study:

- Subjects randomized
- Subjects randomized signing informed consent forms

- Subjects received study drug
- Subjects completed the study
- Subjects who prematurely discontinued study drug
- Subjects who completed study drug
- Reasons for discontinuation of study drug
- Subjects who terminated study prematurely
- Reasons for termination of study

Listings of subjects will be provided for the following categories:

- Subjects who prematurely discontinued study drug
- Subjects who terminated study prematurely
- Subjects who were unblinded to the dose level during the study period
- Subjects who were randomized yet did not receive study drug.

4.3. Treatment Compliance

Study drug compliance rate (%) will be calculated as: 100 * the actual number of days of study drug taken / the supposed number of days of study drug taken. More specifically, the actual number of days of study drug taken will be calculated as the minimum of [Day 10 date, last dose date, and the first primary efficacy outcome date] – first dose date + 1 – dose interruption days up to day 10. The supposed number of days of study drug taken will be calculated as the minimum of [day 10 date, and the first primary efficacy outcome date] - first dose date + 1.

Study drug compliance will be summarized descriptively.

4.4. Extent of Exposure

The number and percentage of subjects who receive study drug will be summarized. Descriptive statistics (N, mean, SD) for study drug duration will be presented for the safety analysis set.

4.5. Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical study. Subjects with major protocol deviations will be identified prior to database lock and the subjects with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn
- Randomized but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose

- Others

4.6. Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before Day 1. Concomitant medications are defined as any therapy used with a period overlapping with the period between the first dose and last dose of study drug, including those that started before and continued after the first dose of study drug.

Summaries of concomitant medications will be presented by anatomic and therapeutic class (ATC) term. The proportion of subjects who receive each concomitant medication will be summarized as well as the proportion of subjects who receive at least 1 concomitant medication. In addition, concomitant medications of special interest will be presented (see Attachment 1).

Prior medications will be summarized by ATC term.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

The primary hypothesis is that JNJ-70033093 reduces the risk of total VTE during the treatment period. This can be achieved by showing either a statistically significant dose-response trend (1-sided 5% significance level) or an event rate for the combined BID groups of JNJ-70033093 that is statistically lower than 30% (1-sided 5% significance level). The family wise error rate will be controlled at 1-sided 10%.

5.1.2. Data Handling Rules

Unless otherwise stated, all efficacy analyses and summaries will be performed using the treatment groups assigned by IWRS.

5.2. Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the total VTE, which is a composite of the proximal DVT (asymptomatic or symptomatic), distal DVT (asymptomatic or symptomatic), non-fatal PE and death.

5.2.1. Analysis Methods

The primary hypothesis, as defined in Section 5.1.1., will be tested with its two components, respectively. The first component, the total VTE event rate lower than 30% in the combined BID doses of JNJ-70033093 in the mITT analysis set and Day 14 analysis period, will be tested at a 1-sided 5% significance level. In other words, the following hypothesis will be tested:

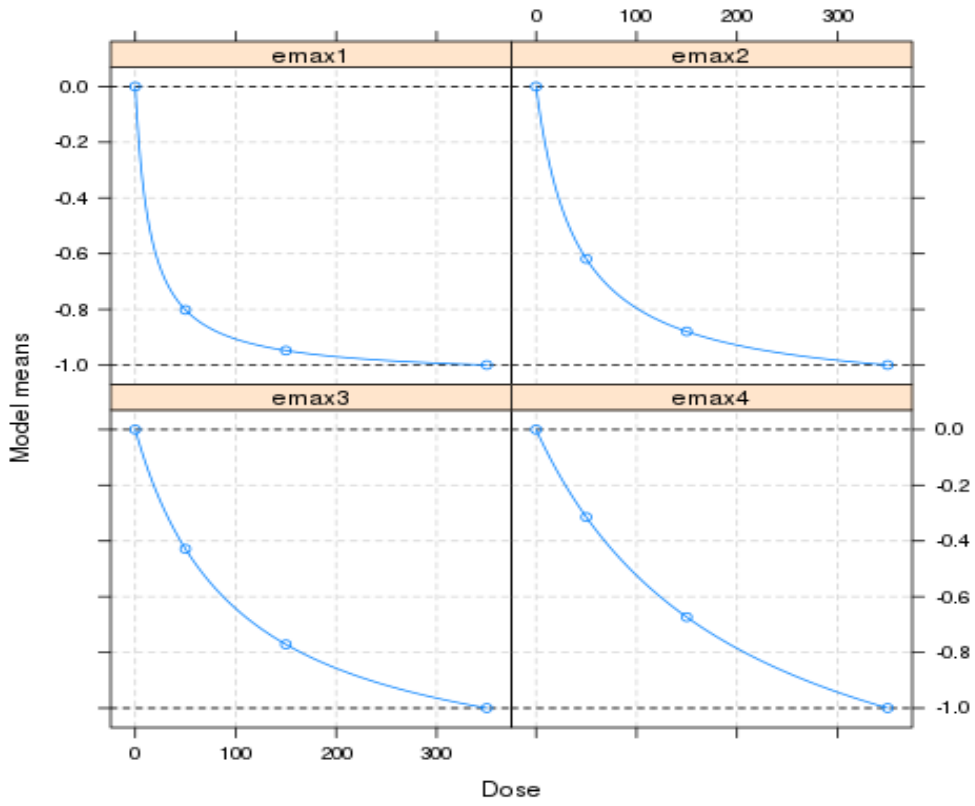
$H_0: Total\ VTE\ Rate \geq 0.3$ Versus $H_1: Total\ VTE\ Rate < 0.3$

Binomial test will be employed to test the hypothesis.

The second component, the dose-response trend test based on the MCP-Mod[1] framework, will consist of contrast tests defined by prespecified candidate models (4 E_{max} dose-response models with varying degrees of ED_{50}, Figure 2), which provide estimates of dose-response (taking BID and once daily into consideration).

The MCP-Mod framework determines a set of optimal model contrasts. Each model will then be evaluated for significance of trend, based on its optimal contrast, resulting in four t-test statistics, one for each candidate model. The t-test statistics will have been adjusted for the fact that multiple candidate models (four) have been included in the trend testing. The efficacy of the drug is then established if the maximum of the t-test statistics exceeds the 95th percentile critical value (one-sided significance level 5%).

Figure 2: Canonical Candidate E_{max} Dose-response Models Used in the MCP-Mod Analysis



5.3. Major Secondary Efficacy Endpoints

Major secondary efficacy endpoints include all individual components of the primary efficacy endpoint

- Proximal DVT
  - Asymptomatic
  - Symptomatic
- Distal DVT

  - Asymptomatic
  - Symptomatic
- Nonfatal PE
- Any death
- Major VTE
  - Proximal DVT
  - Nonfatal PE
  - Any death

5.3.1. Analysis Methods

For the major secondary efficacy endpoints, event rate (incidence) of the total VTE and the individual components in the Day 14 period and the Week 6 period will be summarized by treatment group for the mITT analysis set. The 95% confidence intervals for the relative risk ratio (RR) of each JNJ-70033093 dose group compared with enoxaparin group will also be constructed. The relative risk ratios (RR) and their corresponding confidence intervals will be calculated using Cochran-Mantel-Haenszel method[2,3] with region as a stratification factor.

Additional sensitivity analyses may be explored in ITT, PP, safety population, and/or a subset of the ITT population consisting of subjects with a valid assessment of potential efficacy outcome within Day 14 and/or Week 6 analysis periods.

5.4. Exploratory Efficacy Variable(s)

5.4.1. Definition

The exploratory efficacy variables are defined as

- To evaluate PD to assess its relationships to PK and the relation of these measures to efficacy and safety endpoints (e.g., exposure-response analyses);
- To evaluate exploratory biomarkers to assess their relationship to the probability of total VTE during the treatment period;
- To explore the presence and incidence of asymptomatic MINS as it relates to total knee arthroplasty.

5.4.2. Analysis Methods

The analysis method for the exploratory efficacy variables will be detailed in separate PK and/or PD analysis documents.

6. SAFETY

All safety analyses will be based on the safety analysis set of actual treatment received, unless otherwise specified.

For all continuous safety variables, descriptive statistics will include N, mean and SD. Categorical variables will be summarized using frequency counts and percentages.

6.1. Principal Safety (Bleeding) Endpoint

The principal safety endpoint is any bleeding event, as adjudicated by CEC, which is defined as the composite of major bleeding, clinically relevant non-major (CRNM) bleeding, and minimal bleeding events. Major bleeding refers to the ISTH major bleeding in the surgical setting.

6.1.1. Principal Safety (Bleeding) Analysis Methods

The analysis for safety (bleeding) events has two parts. The first part will focus on the event rate (incidence) within specified study period, which will be implemented by comparing the event rate of each study drug group with the event rate in the enoxaparin group. The analysis method will be the same as the method for major secondary efficacy analysis. Please refer to Section 5.3.1 for details.

The second part of the analysis will be the analysis of time-to-event data. Specifically, analyses based on Kaplan-Meier (K-M) estimates[4] of time from day 1 to the first occurrence of any bleeding event (composite of major, CRNM and minimal bleeding events) will be implemented for each JNJ-70033093 dose group and enoxaparin over the on-treatment period and the Week 6 period.

For the time-to-event analyses, subjects who do not experience any bleeding event during the on-treatment period will be censored at the earliest of the last dose date + 2 days, death date or the last contact date. Similarly, subjects who do not experience any bleeding event during the Week 6 period will be censored at week 6 + 10 days, death date or the last contact date, whichever occurs first.

Frequency distribution of per subject total number of bleeding events will be summarized by dose group using the counts 0, 1, 2 and $\geqslant$ 3.

Sensitivity analyses of bleeding reported by the investigator and/or by comparing the CEC adjudicated event rates in the postoperative period may be presented. Concordance of events between CEC and investigator reported may also be assessed.

Estimation of dose-response relationship in any bleeding will also be assessed by MCP-Mod approach.

6.2. Major Secondary Safety (Bleeding) Endpoints

Major secondary safety (bleeding) endpoints include the following components of the principal safety endpoint,

- Major bleeding,
- Clinically relevant non-major bleeding,
- Clinically relevant bleeding, including both major and non-major,

- Minimal bleeding

6.2.1. Major Secondary Safety (Bleeding) Endpoints Analysis Methods

The statistical analysis method for the major secondary safety (bleeding) endpoints will be similar to the analysis method for the principal safety endpoint. See Section 6.1.1. for details.

6.3. Adverse Event

The verbatim terms used in the eCRF by investigators to identify an AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study drug through the day of last dose plus 2 days is considered as treatment emergent. If the event occurs on the day of the initial administration of study drug, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered as treatment emergent unless it is known to be prior to the first administration of study drug based on the partial date. All reported treatment emergent adverse events (TEAE) will be included in the analysis. For each AE, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summary tables will be provided for:

- All AEs, TEAEs, AEs occurred 2 days after the last dose date, and AEs after the first dose date.
- All SAEs, treatment emergent serious adverse events (TESAEs), and SAEs occurred 2 days after the last dose date, and SAEs after the first dose date.
- AEs leading to discontinuation of study drug
- TEAEs by severity

Incidence of other TEAEs of interest will be summarized.

As per protocol, AEs of interest include bleeding events, wound or joint complications, liver enzyme elevations and clinical liver events. All suspected thrombotic events will also be captured as AEs of interest. Subjects with AEs of interest may be counted or listed using MedDRA SMQs (e.g., hemorrhage excluding laboratory terms SMQ).

Deaths will be displayed by actual treatment received. Frequencies for the following parameters will be included in the summary table:

- Number of subjects who died
- Cause of death
- Relationship to study agent (yes/no)
- A listing of subjects who died.

6.4. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the subjects included in the safety analysis set.

Descriptive statistics will be presented for chemistry, hematology and specific components of urinalysis laboratory tests at scheduled time points.

Changes from baseline to scheduled time points will be summarized for chemistry, hematology and specific components of urinalysis tests and displayed by treatment group.

Number and percentage of subjects with postbaseline clinically important laboratory values and/or markedly abnormal postbaseline values will be presented by treatment group.

Clinically important abnormal laboratory findings to be reported are described below:

- ALT and/or AST (U/L): ≥ 3x ULN.
- Markedly abnormal laboratory findings to be reported are described below:
- ALT and/or AST (U/L) ≥5x ULN
- ALT and/or AST (U/L) ≥ 10x ULN
- Hemoglobin < 80g/L
- Platelet < 50,000/uL

A listing of clinically important and/or markedly abnormal laboratory values will be provided.

6.5. Vital Signs

Vital signs measurements are not being collected in this study.

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1. Pharmacokinetics

PK analyses will be performed on the PK analysis set, defined as subjects who have received at least 1 dose of JNJ-70033093 and have at least 1 valid blood sample drawn for PK analysis.

Descriptive statistics (N, mean, SD, median, range, Coefficient of Variation [CV %] and IQ range) will be used to summarize JNJ-70033093 plasma concentrations at each nominal sampling time point by treatment.

JNJ-70033093 plasma concentrations below the lower limit of quantitation will not be imputed and will be noted in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented.

Population PK analysis using plasma concentration-time data of JNJ-70033093 will be performed using nonlinear mixed-effects modeling. Details will be given in a separate population PK analysis plan and the results of the analysis (including the exposure-response analyses) will be presented in a separate report.

7.2. Pharmacodynamics

PD analyses will be performed on the PD analysis set, defined as subjects who have at least one valid blood sample drawn for PD.

Descriptive statistics (N, mean, SD, median, range, CV (%) and IQ range) will be used to summarize PD response at each nominal sampling time point by treatment group. Changes from baseline will be summarized when applicable.

PD response outside of limit of quantitation will not be imputed and will be noted in the summary statistics.

7.3. Pharmacokinetic/Pharmacodynamic Relationships

Relationships between PD (including aPTT, PT, FXI clotting activity, anti-FXa activity, and TGA) and PK will be evaluated. The relationship between PK and efficacy, as well as between PK and safety endpoints (e.g., exposure-response analyses) will also be evaluated. These analyses will be outlined in a separate population PK analysis plan and reported in a separate population PK report.

8. BIOMARKERS

Descriptive statistics (N, mean, SD, median, range, CV (%) and IQ range) will be used to summarize exploratory biomarker response (including D dimer, high-sensitive cardiac troponin T [hs-cTnT], and FXI antigen) at each nominal sampling time point by treatment group. Changes from baseline will be summarized when applicable.

REFERENCES

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2. Cochran, William G. 1954. “Some Methods for Strengthening the Common Chi-Squared Tests.” *Biometrics* 10 (4). [Wiley, International Biometric Society]: 417–51.
3. Mantel, N., and W. Haenszel. 1959. “Statistical Aspects of the Analysis of Data from Retrospective Studies of Disease.” *Journal of the National Cancer Institute* 22 (4): 719–48.
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ATTACHMENTS

Attachment 1: Medications of Special Interest

Concomitant medications of special interest are defined as follows:

Concomitant Medication Special Interest Category	**Standard ATC Group Name**	ATC Group Code	**Standard Medication Name**	ATC code
ANTITHROMBOTIC AGENTS	Heparin group	B01AB	heparin	B01AB01
			antithrombin III	B01AB02
			dalteparin	B01AB04
			enoxaparin	B01AB05
			nadroparin	B01AB06
			parnaparin	B01AB07
			reviparin	B01AB08
			danaparoid	B01AB09
			tinzaparin	B01AB10
			sulodexide	B01AB11
			bemiparin	B01AB12
	Platelet aggregation inhibitors excl. heparin	B01AC	clopidogrel	B01AC04
			ticlopidine	B01AC05
			acetylsalicylic acid	B01AC06
			dipyridamole	B01AC07
			carbasalate calcium	B01AC08
			iloprost	B01AC11
			abciximab	B01AC13
			eptifibatide	B01AC16
			tirofiban	B01AC17
			treprostinil	B01AC21
			prasugrel	B01AC22
			cilostazol	B01AC23
			ticagrelor	B01AC24
			cangrelor	B01AC25
	Enzymes	B01AD	streptokinase	B01AD01
			alteplase	B01AD02
			anistreplase	B01AD03
			urokinase	B01AD04
			reteplase	B01AD07
			drotrecogin alfa (activated)	B01AD10
			tenecteplase	B01AD10
	Direct thrombin inhibitors	B01AE	desirudin	B01AE01
			lepirudin	B01AE02
			argatroban	B01AE03
			melagatran	B01AE04

Concomitant Medication Special Interest Category	**Standard ATC Group Name**	ATC Group Code	**Standard Medication Name**	ATC code
			ximelagatran	B01AE05
			bivalirudin	B01AE06
			dabigatran etexilate	B01AE07
	Direct factor Xa inhibitors	B01AF	rivaroxaban	B01AF01
			apixaban	B01AF02
			edoxaban	B01AF03
	Other antithrombotic agents	B01AX	defibrotide	B01AX01
			fondaparinux	B01AX05
VITAMIN K AND OTHER HEMOSTATICS	Local hemostatics	B02BC	thrombin	B02BC06
ANTIFIBRINOLYTICS	Amino acids	B02AA	tranexamic acid	B02AA02
			aminocaproic acid	B02AA01
NASAL DECONGESTANTS FOR SYSTEMIC USE	Sympathomimetics	R01BA	phenylpropanolamine	R01BA01
			pseudoephedrine	R01BA02
			phenylephrine	R01BA03
			phenylpropanolamine, combinations	R01BA51
			pseudoephedrine, combinations	R01BA52
OTHER ANALGESICS AND ANTIPYRETICS	Salicylic acid and derivatives	N02BA	carbasalate calcium	N02BA15
			carbasalate calcium combinations excl. psycholeptics	N02BA65
INTESTINAL ANTIINFLAMMATORY AGENTS	Aminosalicylic acid and similar agents	A07EC	sulfasalazine	A07EC01
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	M01A	Butylpyrazolidines	M01AA
			Acetic acid derivatives and related substances	M01AB
			Oxicams	M01AC
			Propionic acid derivatives	M01AE

Concomitant Medication Special Interest Category	**Standard ATC Group Name**	ATC Group Code	**Standard Medication Name**	ATC code
			Fenamates	M01AG
			Coxibs	M01AH
			Other antiinflammatory and antirheumatic agents, non-steroids	M01AX
	ANTIINFLAMMATORY /ANTIRHEUMATIC AGENTS IN COMBINATION	M01B	Antiinflammatory/antirheumatic agents in combination with corticosteroids	M01BA
			Other antiinflammatory/antirheumatic agents in combination with other drugs	M01BX