Janssen Research & Development *

Clinical Protocol

A Randomized, Double-blind, Double-dummy, Multicenter, Adaptive Design, Dose-Escalation (Part 1) and Dose-Response (Part 2) Study to Evaluate the Safety and Efficacy of Intravenous JNJ-64179375 Versus Oral Apixaban in Subjects Undergoing Elective Total Knee Replacement Surgery

TEXT- Targeting EXosite-1 Thrombin Inhibition, TEXT – TKR

Protocol 64179375THR2001; Phase 2
AMENDMENT 1

JNJ-64179375

*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 Pharmaceutica, NV; Janssen, Inc; 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.

This compound is being investigated in Phase 2 clinical studies.

EudraCT NUMBER: 2016-004550-15

Status: Approved
Date: 11 September 2017
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-136897708, 2.0

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

TABLE OF CONTENTS

LIST OF ATTACHMENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	07 Jun 2017
Amendment 1	11 Sep 2017

Amendments below are listed beginning with the most recent amendment.

Amendment 1 (11 September 2017)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall reason for the amendment is to clarify the distribution of normal saline bags and to remove a laboratory test. Normal saline bags will not be provided by the sponsor to all sites because some sites will be providing their own or require local or central distribution.

Applicable Section(s)	Description of Change(s)
Rationale: Removed the text specifying that the sponsor will supply normal saline bags to clarify that sites will provide the normal saline bags unless regulations require local or central distribution.	
14.2. Packaging	Removed the 50-mL normal saline bags.
Rationale: Removed the Hemoclot Thrombin Inhibitor assay because additional testing has now shown that the assay cannot measure levels of JNJ-64179375 below 20 ug/mL and most results will likely be less than this lower limit of quantitation so testing would be of limited value.	
Synopsis, Exploratory Objectives, Synopsis, Exploratory Endpoints; Synopsis, Pharmacodynamic/ Biomarker Evaluations; Synopsis, Statistical Methods; Time and Events Schedule; 2.1.1. Objectives; 2.1.2. Endpoints; 3.2. Study Design Rationale; 9.1.1. Overview (Table 6); 9.4. Pharmacodynamic/ Biomarker Evaluations; 11.6. Pharmacodynamic/Biomarker Analyses; 11.7. Pharmacokinetic/ Pharmacodynamic Analyses	Removed references to the Hemoclot Thrombin Inhibitor assay.
Rationale: Corrected discrepancies in the number of laboratory samples collected between the Time and Events Schedule and Table 6.	
9.1.1. Overview, 9.1.1. Overview (Table 6); 16.1 Study-Specific Design Considerations	Corrected the number of sparse and dense pharmacokinetic (PK) and pharmacodynamic (PD) samples to match the Time and Events Schedule, while separate samples for immunogenicity were removed as the testing can be done on the samples collected for PK. Minor adjustments were also made to the volume of each sample based on the final laboratory supplies to be provided. Total volume was recalculated and updated.
Rationale: Corrected a typographical error.	
11.2. Sample Size Determination	Corrected a typographical error in sample size determination assumptions.

Applicable Section(s)	Description of Change(s)
Rationale: Included language for an impartial witness in the event a subject cannot read and/or write since it had been inadvertently omitted and subjects that cannot read and/or write are not excluded from the study.	
16.2.3. Informed Consent	Included language for an impartial witness in the event a subject cannot read and/or write
Rationale: Modifications have been made for consistency with the current version of the protocol template.	
Throughout the protocol	Template changes have been applied, as appropriate.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or editorial changes were made for clarity.

SYNOPSIS

A Randomized, Double-blind, Double-dummy, Multicenter, Adaptive Design, Dose-Escalation (Part 1) and Dose-Response (Part 2) Study to Evaluate the Safety and Efficacy of Intravenous JNJ-64179375 Versus Oral Apixaban in Subjects Undergoing Elective Total Knee Replacement Surgery

JNJ-64179375 is a first-in-class, recombinant, fully human immunoglobin (Ig) G4 monoclonal antibody that binds reversibly with high affinity and specificity to the exosite-1 region of thrombin. JNJ-64179375 acts as an anticoagulant by blocking only exosite-1-mediated fibrinogen binding to thrombin (and also blocks proteinase-activated receptor-1 binding), but does not inhibit the catalytic activity of the protease. The mechanism of action is distinct from currently available direct thrombin inhibitors that block the active site only (eg, dabigatran, argatroban) or that block both the active site and exosite 1 (eg, bivalirudin, hirudin) and from other mechanisms that inhibit thrombin generation (eg, Factor Xa [FXa] inhibitors). The primary goal of the clinical program will be to demonstrate noninferior efficacy with a reduced bleeding risk versus active comparators. However, the possibility of demonstrating superior efficacy may be considered based on better compliance with a once-monthly dosing regimen and/or the ability to achieve more effective drug levels due to a reduced risk of bleeding (ie, doses not limited by bleeding risk).

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives

Part 1

In men and women undergoing primary unilateral total knee replacement (TKR) surgery, after single-ascending intravenous (IV) doses of JNJ-64179375 or 10 to 14 days of oral apixaban:

Primary Objective

The primary objective is to assess the safety and tolerability of JNJ-64179375 for each dose level for dose escalation within Part 1 and any bleeding events (the composite of major, clinically relevant nonmajor, and minimal bleeding events) for the selection of doses for Part 2.

Secondary Objectives

- To assess the dose response of JNJ-64179375 for the 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 event
- To assess the dose response of JNJ-64179375 for the prevention of total venous thromboembolism (VTE) (proximal and/or distal deep vein thrombosis [DVT, asymptomatic confirmed by venography assessment of the operated leg or objectively confirmed symptomatic], nonfatal pulmonary embolism [PE], or any death) and the individual components of total VTE

Part 2

In men and women undergoing primary unilateral TKR surgery, after a single IV dose of JNJ-64179375 or 10 to 14 days of oral apixaban:

Primary Objective

The primary objective is to assess the efficacy dose response of JNJ-64179375 for the prevention of total VTE (proximal and/or distal DVT [asymptomatic confirmed by venography assessment of the operated leg or objectively confirmed symptomatic], nonfatal PE, or any death).

Key Secondary Objectives

- To assess the dose response of JNJ-64179375 for the 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 event
- To assess the dose response of JNJ-64179375 for the prevention of major VTE (asymptomatic confirmed by venography assessment of the operated leg or objectively confirmed symptomatic proximal DVT, nonfatal PE, or any death) and the individual components of the total VTE endpoint

Common Objectives in Parts 1 and 2

Other Secondary Objectives

- To assess the effect of individual doses of JNJ-64179375 compared with apixaban for both efficacy and safety endpoints, with the goal to identify a studied or model-predicted dose with the most promising benefit-risk profile for a more extensive evaluation in Phase 3
- To assess the effect of JNJ-64179375 compared with apixaban on wound or joint complications in the operated leg

Exploratory Objectives

- To assess the effect of JNJ-64179375 compared with apixaban on other thrombotic events (ie, myocardial infarction [MI], ischemic stroke, peripheral arterial embolism)
- To evaluate the cost effectiveness of JNJ-64179375 compared with apixaban based on health resource utilization
- To assess the pharmacokinetics (PK), pharmacodynamics (PD), and PK/PD relationships of JNJ-64179375 in men and women undergoing primary unilateral TKR surgery and the relation of these measures to efficacy and safety endpoints (eg, exposure-response analyses)
- To evaluate the PD assays (thrombin time [TT], ecarin clotting time [ECT], prothrombin time [PT], activated partial thromboplastin time [aPTT], and D-dimer) to determine the most appropriate tests to measure the effect of JNJ-64179375

Endpoints

The endpoints of the study will be the same for Parts 1 and 2 although the focus of Part 1 will be primarily dose escalation based on safety while the focus of Part 2 will primarily be the assessment of dose response in both safety and efficacy.

Common Endpoints in Parts 1 and 2

Primary Safety Endpoint

The primary safety endpoint is any bleeding event defined as the composite of major, clinically relevant nonmajor, and minimal bleeding events assessed through the Day 10-14 visit.

Primary Efficacy Endpoint

The primary efficacy endpoint is total VTE, defined as the composite of proximal and/or distal DVT (asymptomatic confirmed by venography assessment of the operated leg or objectively confirmed symptomatic), nonfatal PE, or any death assessed through the Day 10-14 visit.

Key Secondary Endpoints

The key secondary endpoints are the assessment of the primary endpoints through the Week 18 visit, and:

- All individual components of the primary safety endpoint (major bleeding, clinically relevant nonmajor bleeding, and minimal bleeding)
- Composite of major and clinically relevant nonmajor bleeding
- Major VTE, a composite of proximal DVT (asymptomatic confirmed by venography assessment of the operated leg or objectively confirmed symptomatic), nonfatal PE, or any death
- All individual components of the primary efficacy endpoint (ie, proximal and/or distal DVT [asymptomatic confirmed by venography assessment of the operated leg or objectively confirmed symptomatic], nonfatal PE, any death)

Other Secondary Endpoints

- Any wound or joint complication in the operated leg

Exploratory Endpoints

- Other thrombotic events (ie, MI, ischemic stroke, peripheral arterial embolism)
- The total length of the initial hospitalization, including the level of care and discharge destination
- The incidence of rehospitalization for any reason
- The number of scheduled and unscheduled visits, including the associated cost to healthcare providers for study outcomes, any other medical reasons, and the diagnostic procedures used in relation to study endpoints
- Calculation of PK parameters, eg, total clearance of the drug after IV administration (CL), volume of distribution (Vd), terminal half-life ($t_{1/2}$), area under the plasma concentration versus time curve from time 0 to infinity (AUC_{inf}), and maximum concentration during a dosing interval (C_{max})
- Changes in PD by dose: TT, ECT, PT, aPTT, and D-dimer
- Changes in PD assays as listed above by concentration metrics (AUC_{inf}, C_{max}, or time-matched concentrations)

Refer to Section 9, Study Evaluations for related evaluations.

Hypothesis

In Part 1, a range of doses of JNJ-64179375 will be assessed to determine if it is sufficiently safe to proceed with Part 2 of the study. No formal hypothesis testing will be conducted for Part 1. In Part 2, the clinical hypothesis is to demonstrate proof-of-efficacy based on the total VTE endpoint. This can be achieved by either showing that JNJ-64179375 has a statistically significant dose-response trend with respect to the total VTE endpoint, or the combined dose groups of JNJ-64179375 have a total VTE event rate of less than 30%.

OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, double-dummy, active-controlled, multicenter, dose-escalation and dose-response study of JNJ-64179375. The study has 2 parts, dose-escalation and dose-response evaluation, and will be conducted in subjects undergoing primary unilateral elective TKR surgery. Part 1 will assess the safety of single-ascending IV doses of JNJ-64179375 while Part 2 will confirm the safety of the doses selected from Part 1 and will assess the efficacy dose-response relationship with respect to the selected doses in the parallel groups. Subjects will participate in either Part 1 or Part 2 of the study only.

For each subject in each part, the study will be conducted in 3 phases: an up to 30-day screening phase before surgery, a 14-day double-blind dosing phase, and a 16-week 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 the subject's participation in Part 1 or Part 2 after randomization will be approximately 18 weeks.

Screening for eligible subjects in Parts 1 and 2 may be done up to 30 days before randomization, pre- or postoperatively. Following primary unilateral elective TKR surgery, eligible subjects will be randomly assigned to treatment with either JNJ-64179375 or apixaban. All subjects will receive a single IV infusion of JNJ-64179375 or JNJ-64179375 placebo and oral apixaban or matching apixaban placebo the day after TKR surgery (Day 1, 0 hours), while the subject is still hospitalized and within 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.

Following discharge or transfer to an alternate facility, subjects in both parts will continue to take apixaban or matching apixaban placebo twice daily to complete a total of 10 to 14 days of dosing. Unilateral venography assessment of the operated leg will be performed after the last dose of apixaban or matching apixaban placebo is taken.

Subjects in both Parts 1 and 2 will return to the site for study-related procedures 5, 10, and 18 weeks after TKR surgery. Safety evaluations will include the monitoring of all nonserious and serious adverse events, (including adverse events of special interest: bleeding events, infusion reactions, hypersensitivity reactions, and wound or joint complications), clinical laboratory tests (ie, hematology, clinical chemistry, urinalysis), vital signs measurements (blood pressure, pulse/heart rate [HR], temperature), and physical examinations. Pharmacokinetics (dense and sparse), PD, and immunogenicity samples will be collected and health resource utilization will also be assessed.

An Operations Committee (OC), Independent Data Monitoring Committee (IDMC), Steering Committee (SC), and independent Clinical Events Committee (CEC) will be commissioned for this study.

The number of cohorts and the size of each cohort in Part 1 may be adjusted based on the ongoing unblinded data review by the OC. Additionally, an unblinded data review is planned for Part 1 after all subjects are expected to have completed the Day 10-14 visit to determine the dose range and doses of JNJ-64179375 for Part 2. An adaptive approach will be used to guide decisions to drop and/or add the doses of JNJ-64179375 and adjust the randomization ratio based on available efficacy, safety, PK, and PD data at 2 planned, unblinded interim analyses in Part 2. The sponsor will also be responsible for conducting an unblinded administrative interim analysis after all subjects are expected to have completed the Day 10-14-visit in Part 2 to facilitate additional study planning.

SUBJECT POPULATION

Subjects will be men and women of non-childbearing potential, at least 50 years of age or older who have undergone an elective primary unilateral TKR and are considered to be medically appropriate for postoperative anticoagulant prophylaxis as determined by the investigator on the basis of the physical examination, medical history, vital signs measurements, and clinical laboratory tests performed as part of screening for elective TKR surgery and any examinations performed as part of standard postoperative care following surgery. It is estimated that approximately 1,500 subjects will be randomly assigned to treatment in this study. Part 1 will include up to approximately 300 subjects and Part 2 is estimated to be 1,200 subjects. Subjects who are withdrawn early from the study will not be replaced.

DOSAGE AND ADMINISTRATION

In both Parts 1 and 2, subjects will be randomly assigned to receive an active single IV dose of JNJ-64179375 or apixaban 2.5 mg given orally twice daily for 10 to 14 days. The administration of the study drugs will begin the day after the TKR surgery (Day 1, 0 hours), while the subject is still hospitalized and within 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. Within that timeframe, both the single IV infusion

and the oral study drug should be administered as close as possible to each other, with up to a maximum of 60 minutes between the start of the IV infusion and the first dose of the oral study drug.

All study drug administrations of JNJ-64179375 must be calculated based on the subject's weight on Day -1 or prior to dosing on Day 1. The single infusion of JNJ-64179375 or JNJ-64179375 placebo (saline) will be administered under the supervision of the investigator or his/her designee over a period of approximately 30 minutes by infusion pump or by gravity flow using a flow regulator. A physician must be immediately available at the study site at all times during the administration of the study drug infusion.

The first dose of apixaban or matching apixaban placebo will be administered as previously described. Subjects will receive apixaban or matching apixaban placebo twice a day while hospitalized and will be given a supply of apixaban or matching apixaban placebo at the time of discharge or transfer to an alternate facility, with instructions to take the study drug orally, twice a day at approximately the same times each day to complete a total of 10 to 14 days of dosing. Apixaban or matching apixaban placebo should be swallowed with water, with or without food.

Part 1 Dosing

Eligible subjects in Part 1 will be randomly assigned to a single-ascending IV dose of JNJ-64179375 or apixaban 2.5 mg given orally twice daily for 10 to 14 days. Six cohorts of up to approximately 50 unique subjects per cohort (total of up to approximately 300 unique subjects) are planned but the number of cohorts and the size of each cohort may be adjusted based on the ongoing unblinded data review by the OC. Within each cohort, subjects will be randomized in a 4:1 ratio to JNJ-64179375 or apixaban, respectively (ie, approximately 40 subjects to JNJ-64179375: approximately 10 subjects to apixaban). JNJ-64179375 will be administered in a dose-escalation manner, with planned doses of 0.3, 0.6, and 1.2 mg/kg in Cohorts 1, 2, and 3, respectively.

- Cohort 1: JNJ-64179375 0.3 mg/kg IV/JNJ-64179375 placebo (saline) IV infusion and matching apixaban placebo/apixaban, orally twice a day for 10 to 14 days
- Cohort 2: JNJ-64179375 0.6 mg/kg IV/JNJ-64179375 placebo (saline) IV infusion and matching apixaban placebo/apixaban, orally twice a day for 10 to 14 days
- Cohort 3: JNJ-64179375 1.2 mg/kg IV/JNJ-64179375 placebo (saline) IV infusion and matching apixaban placebo/apixaban, orally twice a day for 10 to 14 days

The doses of JNJ-64179375 to be used in the optional cohorts will be dependent on the available preliminary safety, tolerability, efficacy, PK, and PD data obtained from the preceding cohorts. Doses within the optional cohorts will either be new doses within the range of 0.1 to 1.8 mg/kg not previously administered in the preceding cohorts, or doses from the preceding cohorts, which may be repeated, as needed.

After all of the subjects in Part 1 are expected to have completed the Day 10-14 visit, an unblinded data review will be conducted by the OC, SC, IDMC, and sponsor to determine the dose range and doses for Part 2.

Part 2 Dosing

Part 2 of this study has an adaptive design, with the intent to optimize data collection for the dose-response evaluation using multiple comparison procedure and modeling (MCP-Mod). Eligible subjects prior to the first interim analysis in Part 2 will be randomly assigned equally to 1 of up to 5 parallel treatment groups, including up to 4 dose levels of JNJ-64179375, given as a single, active IV infusion, or oral apixaban 2.5 mg twice daily for 10 to 14 days. The number of doses and randomization ratio after the 2 interim analyses will depend on the interim analysis results. However, the number of ongoing doses of JNJ-64179375 in the study is not expected to exceed 4 doses.

- Group A: JNJ-64179375 Dose A mg/kg IV and apixaban placebo orally twice a day for 10 to 14 days
- Group B: JNJ-64179375 Dose B mg/kg IV and apixaban placebo orally twice a day for 10 to 14 days
- Group C: JNJ-64179375 Dose C mg/kg IV and apixaban placebo orally twice a day for 10 to 14 days
- Group D: JNJ-64179375 Dose D mg/kg IV and apixaban placebo orally twice a day for 10 to 14 days
- Group E: JNJ-64179375 placebo (saline) IV and apixaban 2.5 mg orally twice a day for 10 to 14 days

EFFICACY EVALUATIONS

Efficacy evaluations will include unilateral venography assessment of the operated leg and assessments of symptomatic DVT, PE, death, or other thrombotic events (ie, MI, ischemic stroke, and peripheral arterial embolism) to assess the primary, secondary, and exploratory efficacy outcomes.

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 of 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.

For all subjects with symptoms of PE, spiral computed tomography (CT), pulmonary angiography, or perfusion/ventilation lung scintigraphy combined with chest radiography will be performed. If a subject is diagnosed with a PE meeting the specified definitions, a subsequent venography assessment of the operated leg is not required.

Other thrombotic events will include MI, ischemic stroke, and peripheral arterial embolism. In addition, events that appear suggestive of study endpoints (eg, transient ischemic attack [TIA], unstable angina) will be reported by the investigator and reviewed by the CEC to ascertain if a thrombotic event has occurred.

PHARMACOKINETIC EVALUATIONS

Samples for analysis of JNJ-64179375 plasma concentration will be collected for all subjects over time as specified in the Time and Events Schedule but will only be analyzed for subjects randomly assigned to JNJ-64179375. Dense PK sampling will be conducted at all sites for subjects at all visits in Part 1 until approximately up to the first 200 subjects have been randomized. Thereafter, the remaining subjects in Part 1 and all subjects in Part 2 will have PK blood samples collected at a limited number of visits (ie, sparse PK sampling). The exact date and time of each PK blood sample collection will be recorded even if the time deviates slightly from the scheduled time of collection. Subjects who experience a bleeding event or symptomatic thrombotic event should have PK samples collected as soon as practically possible after the event occurs.

The PK parameters to be calculated following the single IV dose of JNJ-64179375 will include, but are not limited to, the following: $C_{max,}$ $AUC_{inf,}$ $t_{1/2,}$ CL, and apparent volume of distribution in the terminal phase (V_Z). Additional PK parameters may be determined, as appropriate.

A separate population PK modeling plan will be developed before the first subject is consented and the population PK modeling results will be reported separately, in a document other than the clinical study report (CSR).

IMMUNOGENICITY EVALUATIONS

Blood samples for antibodies to JNJ-64179375 will be collected from all subjects according to the Time and Events Schedule but will only be analyzed in plasma samples for subjects randomized to JNJ-64179375. The exact date and time of each blood sample collection will be recorded. Plasma samples will be screened for antibodies binding to JNJ-64179375 and the titer of confirmed positive samples will be reported. Other analyses (eg, neutralization capacity) may be performed to further characterize the immunogenicity of JNJ-64179375.

PHARMACODYNAMIC/BIOMARKER EVALUATIONS

All subjects will have plasma samples collected to assess PD markers as specified in the Time and Events Schedule. The assay plan is designed to assess target engagement and the mechanism of action with a battery of PD assessments. Pharmacodynamic evaluations will include the coagulation assays (ie, TT, ECT, PT, aPTT) and a D-dimer assessment. Subjects who experience a bleeding event or symptomatic thrombotic event should have PD samples (except D-dimer) collected as soon as practically possible after the event occurs.

SAFETY EVALUATIONS

The safety and tolerability of JNJ-64179375 will be evaluated throughout the study according to the time points provided in the Time and Events Schedule by the assessment of adverse events, including serious adverse events, adverse events of special interest (ie, bleeding events, infusion reactions, hypersensitivity reactions, and wound or joint complications), clinical laboratory tests (ie, hematology, clinical chemistry, urinalysis), vital signs measurements (blood pressure, pulse/HR, temperature), and physical examinations. Safety evaluations may also be performed at unscheduled time points, 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

A total of 1,500 subjects are planned for this study, of which up to 300 subjects will be enrolled in Part 1 and the remainder for the entire study will be enrolled in Part 2. In Part 1, the sample size is not based on hypothesis testing but rather on making a preliminary assessment of the bleeding risk for the doses of JNJ-64179375.

In Part 1, the intent is to escalate across the planned doses (0.3 to 0.6 to 1.2 mg/kg) of JNJ-64179375 based on the OC review of the totality of the data but with a focus on bleeding events. Specific analyses to be reviewed (eg, continual reassessment or escalation with overdose control methods) and dose-escalation decision guidelines will be included in the OC charter. After all subjects in Part 1 are expected to have completed the Day 10-14 visit, an unblinded data review is planned and the selection of the dose range and doses for Part 2 will be based on the evaluation of the totality of the data but with a focus on the any bleeding and total VTE endpoints. Analyses to aid in dose selection will be prespecified in the OC charter and the Part 1 statistical analysis plan (SAP). No formal hypothesis testing is planned for Part 1 due to the limited sample size. Historical apixaban bleeding and VTE event rates may also be considered in making decisions.

In Part 2, this study will use an adaptive design intended to optimize data collection for dose-response modeling. In Part 2, the primary goal is to assess the efficacy (total VTE endpoint) dose-response relationship of JNJ-64179375. A hybrid methodology that combines aspects of multiple testing with modeling techniques (MCP-Mod) will be used for evaluating dose-response trends and estimating the dose-response relationships for the efficacy and bleeding endpoints for JNJ-64179375. The sample size for Part 2 may be adjusted based on the observed bleeding and total VTE event rates in Part 1.

Assuming that 80% of the venography assessments are evaluable and the true underlying total VTE event rates are 15%, 10%, 8%, and 6% at potential doses of JNJ-64179375 of 0.3, 0.6, 0.9, and 1.2 mg/kg,

respectively, with a total sample size of 1,200 subjects, the study is expected to have over 90% power to declare proof-of-efficacy, which is defined as either a statistically significant dose-response trend or a total VTE event rate lower than 30% in the pooled doses of JNJ-64179375 at a 1-sided, 2.5% α-level. The exact power will vary because of the nature of the adaptive study design.

For comparison with apixaban in Part 2, if the true underlying total VTE and any bleeding event rates are as specified in the table below, a simulation study demonstrates that there will be approximately 90% probability to identify a dose within the dose range of 0.3 to 1.2 mg/kg, of which both the model-predicted total VTE and any bleeding event rates met the prespecified noninferiority (NI) criterion (the upper bound of the 1-sided 90% confidence interval [CI] for the odds ratio [JNJ-64179375 to apixaban] is equal to or lower than 1.5 for total VTE and any bleeding events).

Assumed Efficacy and Safety Event Rates by Treatment Group in Sample Size Determination for Part 2

	JNJ-64179375				Apixaban
	0.3 mg/kg	**0.6 mg/kg**	**0.9 mg/kg**	**1.2 mg/kg**	**2.5 mg bid**
Total VTE (Efficacy)	15%	10%	8%	6%	15%
Any Bleeding (Safety)	5%	6%	7%	8%	8%

bid=twice daily; VTE=venous thromboembolism

Two planned, unblinded interim analyses will be conducted in Part 2 by the IDMC as part of the adaptive approach that will be used to guide decisions to drop and/or add doses of JNJ-64179375 and adjust the randomization ratio based on available efficacy, safety, PK, and PD data. A futility analysis will also be included as part of both interim analyses. Further details related to the interim analyses and decision guidelines will be specified in the IDMC charter and Part 2 SAP. In addition, an unblinded administrative interim analysis is planned to be conducted by the sponsor after all subjects are expected to have completed the Day 10-14 visit in Part 2 to facilitate additional study planning.

Plasma concentrations of JNJ-64179375 will be listed for all subjects by time of collection and dose level. For each dose, descriptive statistics, including mean, median, standard deviation (SD), and coefficient of variation will be calculated for the plasma concentrations at each nominal sampling time. In addition, a population PK model will be developed and dependence of PK of JNJ-64179375 on population covariates (eg, demographics, laboratory variables) will be evaluated.

The incidence of antibodies to JNJ-64179375 will be summarized for all subjects who receive a dose of JNJ-64179375 and have at least 1 appropriate sample obtained after study drug administration for the detection of antibodies to JNJ-64179375. A listing of subjects who are positive for antibodies to JNJ-64179375 will be provided. The maximum titers of antibodies to JNJ-64179375 will be summarized for subjects who are positive for antibodies to JNJ-64179375. Analyses of the impact of immunogenicity on PK, PD, PK/PD, efficacy, and safety endpoints will be performed to further characterize the immune responses that are generated.

Descriptive statistics including mean, median, SD, minimum, and maximum will be provided for the PD parameters of TT, ECT, PT, aPTT, and D-dimer. The parameters of TT, PT, and aPTT may be statistically analyzed using mixed models. Other PD parameters may be analyzed similarly.

The PK/PD relationships will be investigated graphically and, if appropriate, may be further analyzed using suitable statistical methods. Preliminary assessments of these relationships will be made available to the IDMC at both interim analyses to support their evaluations.

Health resource utilization will be descriptively summarized by treatment group.

All safety data will be fully listed. The reporting of the safety data of all subjects receiving at least 1 active dose of JNJ-64179375 or apixaban will include the incidence and type of adverse events, plus

absolute values and changes in blood pressure (systolic and diastolic), HR, clinical laboratory data, and physical examinations from predose to the final postdose time point.

Based on the mechanism of action of JNJ-64179375 and given that it is a monoclonal antibody, adverse events of special interest will include bleeding events, infusion reactions, hypersensitivity reactions, and wound or joint complications. Subjects with adverse events of special interest may be counted or listed using standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs) (eg, hemorrhage excluding laboratory terms SMQ). All suspected symptomatic efficacy (thrombotic) events will also be captured as adverse events of special interest.

TIME AND EVENTS SCHEDULE FOR PART 1 AND PART 2

Phase	Screening[a]	Double-Blind Dosing							Follow-up[b]			
		Day 1										
Study Procedures	Up to Day -30	0 h	1 h[c]	4 h	Day 2	Day 3[d]	Day 7[d]	Day 10-14 (EOD/ EW)[e]	Week 5 (±1 wk)	Week 10 (±2 wk)	Week 18 (±2 wk)	Unscheduled Visit[f]
Screening/Baseline/Administrative												
Informed consent[g]	X											
Inclusion/exclusion criteria[h]	X	X										
Medical history and demographics	X											
Bleeding risk history	X											
Relevant prestudy therapy	X											
ECG	X											
Total knee replacement surgery[j]	X											
Study Drug Administration												
Randomization		X										
Dispense/administer study drug[k]		X			X	X	X	X				
Drug accountability								X				
Safety Assessments												
Physical examination[l]	X							X			X	
Vital signs[m]	X	X[i]			X	X	X	X	X	X	X	
Efficacy Assessments												
Venography of the operated leg								X[n]				
Symptomatic thrombotic events[o]		X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Assessments												
Hematology		X[i]			X			X	X		X	
Serum chemistry		X[i]			X			X	X		X	
Urinalysis		X[i]						X	X		X	
Pharmacokinetics/Immunogenicity												
Dense PK sample collection[p]			X	X	X	X	X	X	X	X	X	X
Sparse PK sample collection[q]			X		X			X	X	X	X[r]	X
ADA sample collection		X[i]						X	X	X	X	
Pharmacodynamics												
PD coagulation sample collection[s]		X[i]	X					X	X			X
D-dimer		X[i]						X	X			
Ongoing Subject Review												
Health resource utilization		X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X

Phase	Screening[a]	Double-Blind Dosing							Follow-up[b]			
		Day 1										
Study Procedures	Up to Day -30	0 h	1 h[c]	4 h	Day 2	Day 3[d]	Day 7[d]	Day 10-14 (EOD/ EW)[e]	Week 5 (±1 wk)	Week 10 (±2 wk)	Week 18 (±2 wk)	Unscheduled Visit[f]
Adverse events monitoring, including adverse events of special interest (ie, bleeding events, infusion reactions, hypersensitivity reactions, wound or joint complications)[t]	X	X	X	X	X	X	X	X	X	X	X	X

Key: ADA=antidrug antibody; ECG=electrocardiogram; EOD=end of dosing; EW=early withdrawal; h=hour; PD=pharmacodynamic(s); PK=pharmacokinetic(s); wk=week

[a] Screening for eligible subjects in Parts 1 and 2 may be done up to 30 days before randomization, pre- or postoperatively. Final eligibility must be confirmed **after surgery**, 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] One hour (±10 minutes) from the start of the 30-minute infusion.

[d] Study procedures will be conducted on Days 3 and 7 only for those subjects who are still hospitalized.

[e] Subjects who do not receive the full infusion of JNJ-64179375 or prematurely discontinue dosing (ie, EW) with apixaban or matching apixaban placebo before the end of the double-blind dosing phase will be instructed to return to the study site at the originally scheduled Day 10-14 visit to conduct assessments, including the venography assessment 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 18 assessments.

[f] 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 PD samples (except D-dimer) should be collected as soon as practically possible for any subject who experiences symptomatic thrombotic or bleeding events.

[g] At the time of informed consent, 2 alternative means of contact for the each subject will be collected (eg, contact information of the subject's children, spouse, significant other, caretaker, legal representative, or health care professional).

[h] The investigator will need to determine if the subject is medically appropriate for postoperative anticoagulant prophylaxis on the basis of physical examination, medical history, vital signs measurements, and clinical laboratory tests performed as part of screening for elective TKR surgery and any examination performed as part of standard postoperative care following surgery.

[i] Procedures should be conducted prior to the first dose of the study drug.

[j] Details regarding the total knee replacement (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] The day after TKR surgery (Day 1, 0 hours), while the subject is still hospitalized and within 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, all subjects will receive a single IV infusion of JNJ-64179375 or JNJ-64179375 placebo and oral apixaban or matching apixaban placebo. The first dose of apixaban or matching apixaban placebo will be administered while the subject is hospitalized, with up to a maximum of 60 minutes between the start of the IV infusion and the first dose of oral study drug. Subjects will receive apixaban or matching apixaban placebo twice a day while hospitalized and will be given a supply of apixaban or matching apixaban placebo at the time of discharge or transfer to an alternate facility, with instructions to take the study drug orally, twice a day at approximately the same times each day to complete a total of 10 to 14 days of dosing.

[l] Height and weight should be obtained at the screening visit, with weight only on Day -1 or prior to dosing on Day 1 and the final visit. An assessment of the wound will be made at all visits as part of the adverse event assessment and the final physical examination will assess the range of motion of the operated joint.

[m] Blood pressure and pulse/heart rate (HR) measurements will be assessed with subjects in the supine position with a completely automated device and should be preceded by at least 5 minutes of rest. The subject's temperature should also be obtained.

[n] Subjects who complete dosing with apixaban or matching apixaban placebo will return to the study site for final EOD assessments (at the Day 10-14 visit, EOD), at which time a unilateral venography assessment of the operated leg will be performed within 24 hours of the last dose of apixaban or matching apixaban placebo. If dosing with apixaban or matching apixaban placebo is prematurely discontinued, the venography assessment 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. 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 diagnosed with a PE, a venography assessment of the operated leg is not required.

[o] Suspected symptomatic efficacy (thrombotic) events (DVT, PE, death, myocardial infarction, ischemic stroke, peripheral arterial embolism) will be reported by the investigator and reviewed by the Clinical Events Committee to ascertain if a thrombotic event has occurred.

[p] All sites in Part 1 will collect PK blood samples for subjects at all visits (hereafter referred to as dense PK sample collection) until approximately up to the first 200 subjects have been randomized. The Day 1 samples will be drawn at 1 hour and 4 hours from the start of the IV infusion. The Day 2 blood sample will be drawn 24 hours after the start of the IV infusion and may be done with the subject as an inpatient or outpatient. The Day 3 (48 hours) and Day 7 (144 hours) blood samples are only required for those subjects who are still hospitalized.

[q] After approximately up to the first 200 randomized subjects in Part 1 have initiated dense PK sampling, the remaining subjects in Part 1 and all subjects in Part 2 will have PK blood samples collected at a limited number of visits (hereafter referred to as sparse PK sample collection). The Day 2 sample will be drawn 24 hours after the start of the IV infusion and may be done with the subject as an inpatient or outpatient.

[r] The PK sample will only be collected at this visit if it was not collected at the Week 10 visit.

[s] Pharmacodynamic evaluations will include the coagulation assays (ie, thrombin time [TT], ecarin clotting time [ECT], prothrombin time [PT], and activated partial thromboplastin time [aPTT]). Samples on Day 1 will be obtained before the study drug is administered and at 1 hour after the start of the study drug infusion.

[t] All adverse events, whether serious or nonserious, 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. Adverse events of special interest are bleeding events, infusion reactions, hypersensitivity reactions, and wound or joint complications). All suspected symptomatic efficacy (thrombotic) events will also be captured as adverse events of special interest.

ABBREVIATIONS

ADA	antidrug antibody
aPTT	activated partial thromboplastin time
AV	arteriovenous
CEC	Clinical Events Committee
CI	confidence interval
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
DOAC	direct-acting oral anticoagulants
DVT	deep vein thrombosis
ECG	electrocardiogram
eCRF	electronic case report form
ECT	ecarin clotting time
eDC	electronic data capture
EOD	end of dosing
$FeCl_3$	ferric chloride
FSH	follicle stimulating hormone
FXa	Factor Xa
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HaNDL	Headache and Neurological Deficits with cerebrospinal fluid Lymphocytosis
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	immunoglobin
IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
IWRS	interactive web response system
LMWH	low molecular-weight heparin
MCP-Mod	multiple comparison procedure and modeling
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NI	noninferiority
NSAID	nonsteroidal anti-inflammatory drug
OC	Operations Committee
PCC	prothrombin complex concentrate
PD	pharmacodynamic(s)
PE	pulmonary embolism
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PQC	product quality complaint
PT	prothrombin time
QTcF	QT corrected according to Friderica's formula
RBC	red blood cell
SAD	single-ascending dose
SAP	statistical analysis plan
SC	Steering Committee
SD	standard deviation
SMQ	standardized MedDRA queries
SQ	subcutaneous
SUSAR	suspected unexpected serious adverse reaction

TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TK	toxicokinetic
TKR	total knee replacement
TT	thrombin time
TXA	tranexamic acid
VTE	venous thromboembolism
WBC	white blood cell
wk	week

DEFINITIONS OF PHARMACOKINETIC TERMS

AUC	area under the plasma concentration curve
AUC_{inf}	area under the plasma concentration versus time curve from time 0 to infinity
$AUC_{Day22-29}$	area under the concentration-time curve during the dosing interval between Days 22 and 29
CL	total clearance of drug after IV administration
C_{max}	maximum concentration during a dosing interval
$t_{1/2}$	terminal half-life
T_{max}	time to reach the maximum observed plasma concentration
Vd	volume of distribution
V_Z	apparent volume of distribution in the terminal phase

1. INTRODUCTION

JNJ-64179375 is a first-in-class, recombinant, fully human immunoglobin (Ig) G4 monoclonal antibody that binds reversibly with high affinity and specificity to the exosite-1 region of thrombin. JNJ-64179375 was engineered to mimic the pharmacologic effects of an IgA antibody that was found in a patient with markedly abnormal clotting times but with a lack of spontaneous bleeding episodes over a prolonged follow-up period, representing the profile of an anticoagulant that might have a beneficial therapeutic index in terms of anticoagulation efficacy with low bleeding risk.[1] JNJ-64179375 acts as an anticoagulant by blocking only exosite-1-mediated fibrinogen binding to thrombin (and also blocks proteinase-activated receptor-1 binding), but does not inhibit the catalytic activity of the protease. The mechanism of action is distinct from currently available direct thrombin inhibitors that block the active site only (eg, dabigatran, argatroban) or that block both the active site and exosite 1 (eg, bivalirudin, hirudin) and from other mechanisms that inhibit thrombin generation (eg, Factor Xa [FXa] inhibitors). The primary goal of the clinical program will be to demonstrate noninferior efficacy with a reduced bleeding risk versus active comparators. However, the possibility of demonstrating superior efficacy may be considered based on better compliance with a once-monthly dosing regimen and/or the ability to achieve more effective drug levels due to a reduced risk of bleeding (ie, doses not limited by bleeding risk).

An estimated 920,000 patients in Japan and Europe experience venous thromboembolism (VTE) annually, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE).[6,19] 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.[32] This has led to recommendations in the guidelines that all patients undergoing total knee replacement (TKR) should receive pharmacologic and/or mechanical VTE prophylaxis.[10,19] Low molecular-weight heparin (LMWH) and several direct-acting oral anticoagulants (DOACs), including apixaban, have been used in the prevention of VTE in patients undergoing TKR surgery. However, limitations of these drugs include once- or twice-daily dosing regimens and the possibility of an increased bleeding risk at their recommended dosages.

JNJ-64179375 is being developed for multiple thrombosis-mediated conditions, including the prevention of VTE after TKR surgery, and may offer the potential for equivalent (or superior) efficacy to currently available anticoagulant drugs with a reduced risk of bleeding and a simpler dosing regimen. A novel antithrombotic agent requires the demonstration of both efficacy and safety in relevant populations. Phase 2 studies are frequently performed in subjects undergoing TKR surgery because of the well-documented high incidence of DVT in the absence of adequate thromboprophylaxis, as well as the increased risk of bleeding after recent surgery.[7] An assessment of the effect on efficacy and safety of JNJ-64179375 compared with apixaban in this study will be used to identify an appropriate dose for evaluation in the Phase 3 clinical development program.

For the most comprehensive nonclinical and clinical information regarding JNJ-64179375, refer to the latest version of the Investigator's Brochure (IB) [17] and the Addendum to the IB[18] for JNJ-64179375.

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.

1.1. Background

1.1.1. Nonclinical Studies

1.1.1.1. Nonclinical Pharmacology

JNJ-64179375 binds to human, mouse, rat, and monkey thrombin with high affinity (ie, equilibrium dissociation constants <2 nM) and does not bind to prothrombin or other serine proteases. Spiking of JNJ-64179375 in human plasma in vitro resulted in concentration-dependent prolongation of clotting in various coagulation assays (thrombin time [TT] [dilute and normal], ecarin clotting time [ECT], prothrombin time [PT], and activated partial thromboplastin time [aPTT]), with TT being the most sensitive for this compound. JNJ-64179375 inhibited thrombin-induced platelet aggregation in human platelet-rich plasma in vitro but did not affect platelet aggregation induced by other platelet agonists.

The antithrombotic efficacy of JNJ-64179375 was evaluated in several different thrombosis models in rats and cynomolgus monkeys, and in a human translational ex-vivo flow-chamber model (Badimon chamber). JNJ-64179375 inhibited thrombosis in rat ferric chloride ($FeCl_3$) and arteriovenous (AV)-shunt models of venous thrombosis in a dose-dependent manner (0.1 to 1 mg/kg, intravenous [IV]). At 0.3 and 1 mg/kg, JNJ-64179375 produced antithrombotic efficacy accompanied by approximately 1.5- and 2-fold increases in TT ex vivo, respectively (serum level approximately 7 and 23 µg/mL, respectively). JNJ-64179375 (0.3 and 1 mg/kg, IV) also inhibited thrombosis in a dose-dependent manner in a $FeCl_3$ model of venous thrombosis in cynomolgus monkeys. At the 1-mg/kg dose, serum levels were approximately 40 µg/mL.

The Badimon chamber is a clinical ex-vivo model of thrombosis that mimics the arterial flow conditions within the coronary circulation. Under these conditions, higher concentrations of JNJ-64179375 added extracorporeally to the blood (approximately 250 µg/mL) were required to demonstrate efficacy. Overall, the pharmacology data suggests that the therapeutic range of JNJ-64179375 for the prevention of venous thrombosis may be between approximately 7 µg/mL and 40 µg/mL (ie, the concentrations in rats at the 0.3-mg/kg dose and in monkeys at the 1-mg/kg dose, respectively).

The ability of 4 marketed nonspecific reversal agents (Beriplex®, FEIBA, NovoSeven®, and tranexamic acid [TXA]) to reverse the bleeding induced by JNJ-64179375 was evaluated in the rat-tail transection model. JNJ-64179375 at a dose of 10 mg/kg IV, (ie, a 10-fold higher dose than the effective dose in the $FeCl_3$ and AV-shunt models of venous thrombosis), resulted in increases in bleeding time and blood loss in this model; however, these increases in bleeding parameters were significantly attenuated by pretreatment with either Beriplex (a 4-factor

prothrombin complex concentrate [PCC]) or FEIBA (an activated PCC). In contrast, TXA and NovoSeven did not shorten the bleeding times after dosing with JNJ-64179375 at the doses studied.

1.1.1.2. Safety Pharmacology

Safety pharmacology evaluations were incorporated into the 1-month repeat-dose Good Laboratory Practice (GLP) toxicology studies in rats (T-2016-006) and cynomolgus monkeys (T-2016-005). The results of the 1-month GLP toxicity study in monkeys with JNJ-64179375 (3, 15, 50 mg/kg/week [wk]) IV and 30 mg/kg/wk subcutaneous [SQ]) indicated no treatment-related abnormalities in rhythm or waveform morphology at any dose level based on comparison of predose and postdose electrocardiogram (ECG) recordings, and the ECGs evaluated in this study were qualitatively considered normal for cynomolgus monkeys. In the monkey study, there were no treatment-related changes in blood pressure, heart rate (HR), respiratory rate, or body temperature. Clinical observations from both the rat (up to 30 mg/kg/wk) and monkey studies did not reveal any treatment-related neurobehavioral effects.

1.1.1.3. Toxicology

A series of in-vitro and in-vivo nonclinical studies were conducted as part of the JNJ-64179375 safety assessment in support of clinical studies with a treatment period up to 1 month. Both the rat and cynomolgus monkey are pharmacologically relevant species for toxicology testing. The maximum dose tested in the non-GLP studies in rats and monkeys was 100 mg/kg/wk IV, and in GLP studies, 30 mg/kg/wk and 50 mg/kg/wk in rats and monkeys, respectively. In these 1-month repeat-dose studies, animals did not demonstrate any overt or target organ toxicities upon administration of JNJ-64179375 other than those related to an extension of the intended pharmacology, including dose-dependent prolongation in PT, aPTT, and TT, bruises and hemorrhage at the site of administration (rats only), increased hold-off times (bleeding stop time) after venipuncture (monkeys), and mortality (rat only).

Five of 8 mortalities observed in the non-GLP and GLP rat studies occurred in the toxicokinetic (TK) animals that had blood samples collected from the jugular vein repeatedly throughout the in-life phases. The 2 main study rats in the non-GLP study died either on the day of or the morning after blood sampling. In the GLP study (no blood sampling in main study animals), the death of 1 main study rat in the 10-mg/kg dose group represented 1 in 90 rats at the same or higher doses (10-mg/kg IV, 30-mg/kg IV, and SQ groups). However, there were no histopathological findings in any of the tissues and organs examined. In addition, there were no histopathological findings in any rats examined at the end-of-dosing phase. Therefore, it can be concluded that the mortalities in rats are most likely related to study procedures in anticoagulated animals and not directly due to treatment with JNJ-64179375.

Excluding the pharmacological effects, the no-observable-adverse-effect-level was defined at the highest doses tested in the 1-month GLP studies; 30 mg/kg/wk IV for the rat and 50 mg/kg/wk IV for the monkey, respectively. The corresponding exposures were: rat maximum concentration during a dosing interval (C_{max}) at 1,241 µg/mL and area under the concentration-time curve during the dosing interval between Day 22 and Day 29 ($AUC_{Day22-29}$) at

4,607 µg•day/mL; monkey C_{max} at 2,853 µg/mL and $AUC_{Day22-29}$ at 11,962 µg•day/mL (both area under the plasma concentration curve [AUC] values were from the last dose interval, Days 22-29).

1.1.1.4. Pharmacokinetic and Product Metabolism in Animals

Single-dose pharmacokinetic (PK) studies were conducted in rats and cynomolgus monkeys and multiple-dose TKs were assessed in the 1-month non-GLP and GLP rat and cynomolgus monkey toxicology studies. In the single-dose PK studies in rats, the drug exposure increased with dose in an approximately dose-proportional manner following a single IV dose in the dose range from 0.1 to 10 mg/kg. In cynomolgus monkeys, the C_{max} increased with dose in an approximately dose-proportional manner, but the dose-normalized area under the concentration-time curve from time zero to infinity (AUC_{inf}) increased with dose in a more than dose-proportional manner following a single IV dose ranging from 0.3 to 10 mg/kg. The maximum concentration occurred at 3 to 5 days postdose and the estimated absolute bioavailability was 61.40% to 70.40% following administration of a single SQ dose of JNJ-64179375 of 1 mg/kg and 3 mg/kg, respectively, in rats. Following administration of a single SQ dose of JNJ-64179375 (3 mg/kg) in monkeys, the maximum concentration occurred at 3 days postdose, and the absolute bioavailability was nearly complete.

In the single-dose PK studies in rats, the mean total clearance of drug after IV administration (CL) of JNJ-64179375 from the 0.1- to 10-mg/kg IV-dose groups ranged from 3.95 to 6.44 mL/day/kg, and the mean terminal half-life ($t_{1/2}$) ranged from 9.64 to 13.44 days across all dose groups. The mean CL of JNJ-64179375 from the IV-dose groups ranged from 1.81 to 4.82 mL/day/kg, and the mean values of $t_{1/2}$ ranged from 7.2 to 17.3 days across all dose groups in monkeys. The mean apparent volume of distribution in the terminal phase (V_z) of JNJ-64179375 ranged from 53.07 to 94.46 mL/kg across the 0.1- to 10-mg/kg single IV dose groups in rats. The mean V_z of JNJ-64179375 following a single IV dose ranged from 26.32 to 62.26 mL/kg across all dose groups in monkeys. The V_z of JNJ-64179375 in rats and cynomolgus monkeys was similar to the blood volume in each species, suggesting that JNJ-64179375 was mainly distributed in the intravascular space in rats and monkeys.

In the 1-month non-GLP and GLP repeat-dose studies in rats and monkeys, the drug exposure increased with dose in an approximately dose-proportional manner following weekly IV administration of JNJ-64179375 (3 to 100 mg/kg). The mean drug accumulation ratios ranged from approximately 1.5- to 3-fold in the systemic circulation following weekly IV or SQ administration of JNJ-64179375 in rats and monkeys, indicating moderate drug accumulation.

Some rats and cynomolgus monkeys exhibited faster decreases in serum concentrations of JNJ-64179375 during the terminal phase following single or repeated administration of JNJ-64179375. It is likely that the relatively rapid clearance and short half-life in some rats and cynomolgus monkey was due to the impact of antidrug antibodies (ADAs) on PK but the formal analysis has not yet been completed. No apparent differences in drug exposure were observed

between female and male rats following weekly IV or SQ doses of JNJ-64179375 in both non-GLP and GLP toxicology studies.

1.1.2. Clinical Studies

The safety, tolerability, PK, immunogenicity, and pharmacodynamics (PD) of single-ascending IV and SQ doses of JNJ-64179375 are currently being evaluated in a first-in-human study (Protocol 64179375EDI1001). Interim data from this study are included in the Addendum to the IB.[18] The study was initiated in November 2016 and is being conducted at a single study site in Belgium.

1.1.2.1. Overall Study Design and Status

The study is ongoing, has 3 parts, and is being conducted in healthy male subjects: Part 1 assesses the safety, tolerability, PK, immunogenicity, and PD of single-ascending IV doses of JNJ-64179375; Part 2 assesses the reversibility of the PD effects of JNJ-64179375 following a single IV dose of a 4-factor PCC, as well as safety, tolerability, PK, and immunogenicity; and Part 3 assesses the safety, tolerability, PK, immunogenicity, and PD of a single SQ dose of JNJ-64179375.

In Part 1, up to 6 cohorts of 8 subjects each were to be enrolled to evaluate successively increasing doses of JNJ-64179375 over a dose range of 0.03 to 5.0 mg/kg (planned doses of 0.03, 0.1, 0.3, 1.0, 2.5, and 5.0 mg/kg). Up to 2 additional optional cohorts could be enrolled to repeat a dose or examine other doses. In Parts 2 and 3, 1 cohort of 8 subjects was to be enrolled in each.

In Parts 1 and 3 of the study, 6 of the 8 subjects to be enrolled in each cohort were to be randomly assigned to treatment with JNJ-64179375 and 2 subjects were to be randomly assigned to treatment with placebo. In Part 2, all 8 subjects were to receive JNJ-64179375 followed by either 4-factor PCC (n=6) or placebo (n=2). For each subject in each part, the study consists of a screening period (up to 28 days), an in-house period (15 days/14 nights), and an outpatient period (approximately 99 days), with the total study duration up to approximately 22 weeks for each subject.

1.1.2.2. Part 1

The preliminary results presented below are based on unblinded data from a planned interim analysis that was conducted after all Part 1 subjects completed the in-house period (data cutoff 5 April 2017).

1.1.2.2.1. Demographic Characteristics

In Part 1, the mean age of the subjects was 32.7 years (range 19 to 45 years) and the mean weight was 81.24 kg (range 60.2 to 100.3 kg). Over 90% of the subjects were Caucasian. There were no meaningful differences between the cohorts for any demographic parameter.

1.1.2.2.2. Safety and Tolerability

The actual dose sequence in Part 1 (8 cohorts) was 0.03, 0.1, 0.3, 1.0, 2.5, repeat 2.5, 1.75, and 2.125 mg/kg (total n=63 subjects: JNJ-64179375=48 subjects, placebo=15 subjects). After the dose was escalated to 2.5 mg/kg of JNJ-64179375 or placebo as planned, an increased frequency and severity of bleeding-related adverse events were observed, which suggested a potential bleeding-risk signal. To further characterize the safety/tolerability of the 2.5-mg/kg dose of JNJ-64179375, an additional 8 subjects were enrolled to repeat the JNJ-64179375 2.5-mg/kg or placebo dose cohort. Based on the safety and tolerability data pooled from the two 2.5-mg/kg cohorts (Cohorts 5 and 6), 2.5 mg/kg of JNJ-64179375 was assessed as a dose with a bleeding signal and therefore the planned 5-mg/kg dose of JNJ-64179375 was not studied. Instead, the 2.5-mg/kg dose was de-escalated to 1.75 mg/kg (Cohort 7) and then a dose of 2.125 mg/kg (Cohort 8) was completed as the last dose cohort studied in Part 1.

Single-ascending IV doses of JNJ-64179375 have been generally well tolerated in healthy male subjects over the dose range of 0.03 to 2.5 mg/kg. No subject has withdrawn from the study due to an adverse event. A summary of the most frequent treatment-emergent adverse event (TEAE) preferred terms (>5% incidence for placebo and the JNJ-64179375 groups combined) is provided in Table 1. Overall, most subjects experienced at least 1 TEAE (placebo, 80%; JNJ-64179375 dose groups combined, approximately 90%), with no clear dose relationship for nonbleeding adverse events. The most frequent nonbleeding TEAEs were headache (placebo 33.3%, JNJ-64179375 22.9%), laceration (placebo 6.7%, JNJ-64179375 20.8%), and diarrhoea (placebo 13.3%, JNJ-64179375 12.5%). Most TEAEs were assessed by the investigator as mild in intensity. Three events were assessed as severe in intensity (meningitis viral, subsequently diagnosed as Headache and Neurological Deficits with cerebrospinal fluid Lymphocytosis [HaNDL] syndrome, metabolic acidosis, and pneumonia aspiration) in the 2 subjects with serious adverse events as described below.

Three serious adverse events considered doubtfully related to the study drug were reported for 2 subjects. Metabolic acidosis and panic attack were reported for 1 subject who had personal problems related to a relationship. The subject had a prior history of anxiety and alcohol abuse that were not disclosed at the screening visit. The subject was hospitalized on Study Day 18 after drinking a liter of vodka. He was admitted to the intensive care unit for the treatment of metabolic acidosis and aspiration pneumonia. After transferring to the psychiatric unit for alcohol treatment, he signed himself out against medical advice. The second subject was hospitalized on Study Day 82, with a headache, fever, neurological symptoms, and a preliminary diagnosis of viral meningitis. The majority of the workup was negative (clinical laboratory reports, polymerase chain reaction for herpes virus, magnetic resonance imaging, and electroencephalogram) except for the lumbar puncture, which revealed white blood cells (WBCs) (330 per µl) and protein. The subject received symptomatic treatment and was discharged. Five days later (Study Day 91), the subject was readmitted and a diagnosis of HaNDL syndrome was made (after the interim analysis data cutoff date). The symptoms improved and the subject was discharged.

Table 1: Most Frequent (>5% Incidence) Treatment-Emergent Adverse Events - by Body System and Preferred Term: Part 1; Safety Analysis Set (Study 64179375EDI1001)

		JNJ-64179375							
	Plc	0.03mg/kg	0.1mg/kg	0.3mg/kg	1.0mg/kg	1.75 mg/kg	2.125 mg/kg	2.5mg/kg	Active Total
Subjects treated	15	6	6	6	6	6	6	12	48
Subjects with 1 or more AEs	12 (80%)	5 (83.3%)	6 (100%)	6 (100%)	5 (83.3%)	4 (66.7%)	6 (100%)	11 (91.7%)	43 (89.6%)
Body System or Organ Class/ Dictionary-Derived Term									
General disorders and administration site conditions	8 (53.3%)	2 (33.3%)	3 (50%)	2 (33.3%)	2 (33.3%)	4 (66.7%)	6 (100%)	9 (75%)	28 (58.3%)
Vessel puncture-site bruise	2 (13.3%)	0	2 (33.3%)	2 (33.3%)	2 (33.3%)	4 (66.7%)	6 (100%)	7 (58.3%)	23 (47.9%)
Fatigue	2 (13.3%)	1 (16.7%)	1 (16.7%)	0	0	0	0	0	2 (4.2%)
Influenza like illness	3 (20%)	0	1 (16.7%)	0	0	0	0	0	1 (2.1%)
Gastrointestinal disorders	5 (33.3%)	4 (66.7%)	3 (50%)	2 (33.3%)	0	0	3 (50%)	7 (58.3%)	19 (39.6%)
Gingival bleeding	2 (13.3%)	2 (33.3%)	1 (16.7%)	2 (33.3%)	0	0	2 (33.3%)	3 (25%)	10 (20.8%)
Diarrhoea	2 (13.3%)	2 (33.3%)	2 (33.3%)	0	0	0	0	2 (16.7%)	6 (12.5%)
Abdominal pain	0	2 (33.3%)	1 (16.7%)	0	0	0	1 (16.7%)	1 (8.3%)	5 (10.4%)
Nausea	1 (6.7%)	1 (16.7%)	0	0	0	0	2 (33.3%)	0	3 (6.3%)
Injury, poisoning and procedural complications	2 (13.3%)	1 (16.7%)	4 (66.7%)	2 (33.3%)	3 (50%)	1 (16.7%)	1 (16.7%)	6 (50%)	18 (37.5%)
Laceration	1 (6.7%)	0	2 (33.3%)	0	3 (50%)	1 (16.7%)	1 (16.7%)	3 (25%)	10 (20.8%)
Contusion	2 (13.3%)	0	1 (16.7%)	2 (33.3%)	0	0	0	1 (8.3%)	4 (8.3%)
Nervous system disorders	5 (33.3%)	1 (16.7%)	3 (50%)	2 (33.3%)	1 (16.7%)	3 (50%)	2 (33.3%)	3 (25%)	15 (31.3%)
Headache	5 (33.3%)	1 (16.7%)	1 (16.7%)	2 (33.3%)	0	2 (33.3%)	2 (33.3%)	3 (25%)	11 (22.9%)
Respiratory, thoracic and mediastinal disorders	6 (40%)	4 (66.7%)	0	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	4 (33.3%)	12 (25%)
Epistaxis	3 (20%)	1 (16.7%)	0	1 (16.7%)	1 (16.7%)	0	0	2 (16.7%)	5 (10.4%)
Cough	2 (13.3%)	2 (33.3%)	0	0	0	0	0	0	2 (4.2%)
Infections and infestations	5 (33.3%)	2 (33.3%)	5 (83.3%)	0	1 (16.7%)	0	1 (16.7%)	0	9 (18.8%)
Nasopharyngitis	2 (13.3%)	0	2 (33.3%)	0	1 (16.7%)	0	1 (16.7%)	0	4 (8.3%)
Investigations	1 (6.7%)	2 (33.3%)	2 (33.3%)	1 (16.7%)	1 (16.7%)	0	0	3 (25%)	9 (18.8%)
Blood creatine phosphokinase increased	1 (6.7%)	1 (16.7%)	0	0	1 (16.7%)	0	0	1 (8.3%)	3 (6.3%)

AEs= adverse events; Plc=placebo
Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects, not the number of events.
Reported dictionary version: MedDRA 19.1.

[TSFAE01P1.RTF] [JNJ-64179375\EDI1001\DBR_IA_SEQUESTERED\RE_IA_SEQUESTERED\PREPROD\TSFAE01P1.SAS] 25APR2017, 15:30

Table 2 shows all treatment-emergent bleeding adverse events selected using the Medical Dictionary for Regulatory Activities (MedDRA) standardized MedDRA queries (SMQ) term hemorrhage (excluding laboratory terms). In the placebo group, 46.7% of the subjects had 1 or more events compared with 72.9% for the combined JNJ-64179375 groups. This difference was mostly due to the increased incidence of treatment-emergent bleeding adverse events observed in the 2.125- (100%) and 2.5- (91.7%) mg/kg groups.

The most common bleeding adverse events observed were vessel puncture-site bruises (placebo, 13.3%; JNJ-64179375, 47.9%), gingival bleeding (placebo, 13.3%; JNJ-64179375, 20.8%), and epistaxis (placebo, 20%; JNJ-64179375, 10.4%). Most treatment-emergent bleeding adverse events were associated with mild trauma (ie, venipuncture, brushing teeth/gums, blowing nose) and all resolved. All were considered mild in intensity except for 6 events considered to be of moderate intensity (1 event of epistaxis at 1 mg/kg, 1 event of ecchymosis at 2.125 mg/kg, and 4 skin-bruising or hematoma events at 2.5 mg/kg). The criteria for moderate intensity were defined as an episode of epistaxis lasting more than 5 minutes or a skin bruise event with a maximum dimension of 10 cm or larger.

Table 2: Treatment-Emergent Bleeding Adverse Events - by Body System and Preferred Term: Part 1; Safety Analysis Set (Study 64179375EDI1001)

		JNJ-64179375							
	Plc	0.03 mg/kg	0.1 mg/kg	0.3 mg/kg	1.0 mg/kg	1.75 mg/kg	2.125 mg/kg	2.5 mg/kg	Active Total
Subjects treated	15	6	6	6	6	6	6	12	48
Subjects with 1 or more Bleeding AEs	7 (46.7%)	3 (50%)	5 (83.3%)	4 (66.7%)	2 (33.3%)	4 (66.7%)	6 (100%)	11 (91.7%)	35 (72.9%)
Body System or Organ Class Dictionary-Derived Term									
General disorders and administration site conditions	3 (20%)	0	2 (33.3%)	2 (33.3%)	2 (33.3%)	4 (66.7%)	6 (100%)	8 (66.7%)	24 (50%)
Vessel puncture site bruise	2 (13.3%)	0	2 (33.3%)	2 (33.3%)	2 (33.3%)	4 (66.7%)	6 (100%)	7 (58.3%)	23 (47.9%)
Infusion site bruising	1 (6.7%)	0	0	0	0	0	0	2 (16.7%)	2 (4.2%)
Catheter site haemorrhage	0	0	0	0	0	0	0	1 (8.3%)	1 (2.1%)
Infusion site haematoma	0	0	0	0	0	0	0	1 (8.3%)	1 (2.1%)
Injection site bruising	0	0	0	0	0	0	0	1 (8.3%)	1 (2.1%)
Vessel puncture site haematoma	0	0	0	0	0	0	1 (16.7%)	0	1 (2.1%)
Gastrointestinal disorders	2 (13.3%)	3 (50%)	1 (16.7%)	2 (33.3%)	0	0	2 (33.3%)	4 (33.3%)	12 (25%)
Gingival bleeding	2 (13.3%)	2 (33.3%)	1 (16.7%)	2 (33.3%)	0	0	2 (33.3%)	3 (25%)	10 (20.8%)
Haematochezia	0	0	0	0	0	0	0	1 (8.3%)	1 (2.1%)
Mouth haemorrhage	0	1 (16.7%)	0	0	0	0	0	0	1 (2.1%)
Injury, poisoning and procedural complications	2 (13.3%)	1 (16.7%)	1 (16.7%)	2 (33.3%)	0	0	0	2 (16.7%)	6 (12.5%)
Contusion	2 (13.3%)	0	1 (16.7%)	2 (33.3%)	0	0	0	1 (8.3%)	4 (8.3%)
Procedural haemorrhage	0	1 (16.7%)	0	0	0	0	0	0	1 (2.1%)
Traumatic haemorrhage	0	0	0	0	0	0	0	1 (8.3%)	1 (2.1%)
Respiratory, thoracic and mediastinal disorders	3 (20%)	1 (16.7%)	0	1 (16.7%)	1 (16.7%)	0	0	2 (16.7%)	5 (10.4%)
Epistaxis	3 (20%)	1 (16.7%)	0	1 (16.7%)	1 (16.7%)	0	0	2 (16.7%)	5 (10.4%)
Skin and subcutaneous tissue disorders	2 (13.3%)	0	0	0	0	0	1 (16.7%)	1 (8.3%)	2 (4.2%)
Ecchymosis	1 (6.7%)	0	0	0	0	0	1 (16.7%)	0	1 (2.1%)
Blood blister	1 (6.7%)	0	0	0	0	0	0	0	0
Skin haemorrhage	0	0	0	0	0	0	0	1 (8.3%)	1 (2.1%)
Investigations	0	1 (16.7%)	1 (16.7%)	0	0	0	0	1 (8.3%)	3 (6.3%)
Blood urine present	0	1 (16.7%)	1 (16.7%)	0	0	0	0	1 (8.3%)	3 (6.3%)
Ear and labyrinth disorders	0	0	0	0	0	0	1 (16.7%)	0	1 (2.1%)
Ear haemorrhage	0	0	0	0	0	0	1 (16.7%)	0	1 (2.1%)

AE=adverse event; Plc=placebo

Note: Percentages calculated with the number of subjects in each group as denominator.

Note: Incidence is based on the number of subjects, not the number of events.

Reported dictionary version: SMQ19.1, HAEMORRHAGE TERMS (EXCL LABORATORY TERMS) (SMQ)

[TSFAE02P1.RTF] [JNJ-64179375\EDI1001\DBR_IA_SEQUESTERED\RE_IA_SEQUESTERED\PREPROD\TSFAE02P1.SAS] 25APR2017, 15:30

Clinical Laboratory, Vital Signs, and ECG Assessments

Clinical safety laboratory tests (clinical chemistry, hematology, coagulation, and urinalysis), vital signs, and ECGs were collected at specified times before and after study drug dosing.

There were no apparent group-mean trends or dose-related effects in these assessments with JNJ-64179375, with the exception of dose-related increases in PT, aPTT, and TT levels consistent with the mechanism of action of JNJ-64179375 (see Section 1.1.2.2.4, Pharmacodynamics). Individual ECGs did not show any clinically significant changes from baseline; no subject had a QT corrected according to Fridericia's formula (QTcF) >450 msec or an increase from baseline in QTcF >30 msec.

1.1.2.2.3. Pharmacokinetics

The results presented below are based on preliminary bioanalytical data and nominal sampling times from the subjects who received at least 1 dose of JNJ-64179375 in Part 1. Plasma samples were analyzed to determine concentrations of JNJ-64179375 using a validated, selective, and sensitive immunoassay method (lower limit of quantification 0.01 µg/mL). Interim preliminary PK results were determined using noncompartmental methods and are summarized in Table 3.

Table 3: Mean (±SD) Pharmacokinetic Parameters of JNJ-64179375 Following a Single 30-minute IV Infusion (0.03 to 2.5 mg/kg, Part 1) in Healthy Male Subjects

Cohort	JNJ-64179375 mg/kg IV	C_{max} µg/mL	T_{max}[a] h	AUC_{inf} day*µg/mL	CL mL/day/kg	V_z mL/kg	$t_{1/2}$ day
1	0.03	0.707 (0.196)	1 (0.5-1)	15.4 (3.87)	2.07 (0.628)	73.3 (21.8)	24.7 (3.6)
2	0.1	2.15 (0.183)	1 (0.5-8)	47.2 (6.74)	2.16 (0.361)	76.3 (5.67)	24.8 (3.2)
3	0.3	6.86 (1.30)	1 (0.5-4)	145 (22.3)	2.11 (0.286)	78.8 (19.1)	26.0 (5.3)
4	1	28.4 (3.90)	1 (0.5-4)	514 (71.3)	1.98 (0.285)	83.0 (11.5)	29.2 (3.1)
5+6	2.5	58.0 (12.7)	2.5 (0.5-8)	1266 (266)	2.06 (0.487)	80.5 (12.4)	27.8 (5.2)
7	1.75	44.3 (8.90)	2.5 (0.5-4)	813 (124)	2.20 (0.328)	68.7 (9.64)	21.8 (2.1)
8	2.125	42.9 (3.62)	1 (0.5-4)	970 (209)	2.28 (0.499)	73.5 (15.3)	23.2 (6.9)

AUC_{inf}=area under the concentration curve from zero to infinity; CL= total clearance of drug after IV administration; C_{max}= maximum concentration during a dosing interval; h=hour; IV=intravenous; SD=standard deviation; $t_{1/2}$=terminal half-life; T_{max}=time to reach the maximum observed plasma concentration; Vz=apparent volume of distribution in the terminal phase
[a]Data presented as Median (Minimum-Maximum)

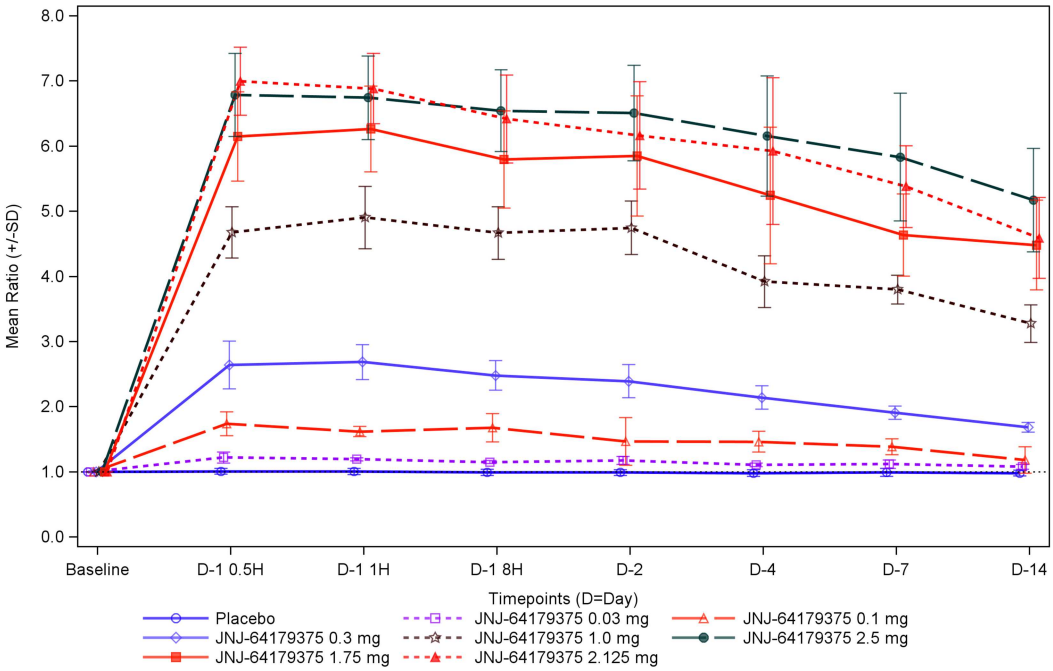
The median time to reach the maximum observed plasma concentration (T_{max}) was 1 to 2.5 hours postdose. The mean C_{max} and AUC_{inf} increased in an approximately dose-proportional manner. The mean $t_{1/2}$ ranged from approximately 21.8 to 29.2 days.

1.1.2.2.4. Pharmacodynamics

Prothrombin time, aPTT, and TT demonstrated dose-dependent increases whether measured locally or at a central specialty laboratory, with TT being the most sensitive test and PT the least sensitive test. A plot of mean ratio to baseline for TT from the central specialty laboratory is provided in Figure 1. For TT, the 2 highest dose groups showed similar prolongations for the early timepoints (an approximately 7-fold increase) as some subjects in both groups exceeded the laboratory upper reporting limit of 120 seconds. At 14 days, the prolongation in TT was about 5-fold for the highest dose group. At the 0.3-mg/kg dose level, the peak prolongation in TT was

approximately 2.7-fold and it was approximately 1.7-fold at 14 days. For aPTT, the assay upper reporting limit was not approached for any subject but the maximum prolongation appears to be an approximately 1.6-fold increase from baseline for each of the 3 highest dose groups. For PT, the maximum-fold increase was approximately 1.3-fold at the highest dose. These data are consistent with the in-vitro data and with the mechanism of action of JNJ-64179375. Local laboratory results demonstrated a similar pattern.

Figure 1: Thrombin Time (s) Mean Ratio to Baseline by Treatment Group Central Specialty Laboratory; Safety Analysis Set (Study 64179375EDI1001)



Baseline is defined as the last valid measurement prior to dosing.

[GSFEPDC1.RTF] [JNJ-64179375\EDI1001\DBR_IA_SEQUESTERED\RE_IA_SEQUESTERED\PREPROD\GSFEPDC1.SAS] 30MAY2017, 12:09

1.1.2.2.5. Overall Summary

In this single-ascending dose (SAD), randomized, double-blind, placebo-controlled study in healthy male subjects (Part 1), JNJ-64179375 was generally well tolerated at all doses. All observed bleeding events were of mild or moderate intensity, mostly related to local trauma (eg, venipuncture, brushing teeth, blowing nose), and none were severe or serious. At the 2 highest doses (2.125 and 2.5 mg/kg), an increased frequency (and severity at 2.5 mg/kg) of bleeding events was observed compared with placebo.

With the exception of the bleeding adverse events, there was no evidence of dose-dependent adverse events over the studied dose range. As hypersensitivity reactions have been observed with the administration of monoclonal antibodies, infusion or allergic reactions were closely monitored for this study. One subject in the 2.5-mg/kg cohort developed mild urticaria that started prior to receiving the study drug. The urticaria spread and was assessed as moderate in severity at approximately 4 hours postdose. The urticaria resolved spontaneously 24 hours later and was considered doubtfully related to the study drug.

JNJ-64179375 administered as an IV infusion exhibited a favorable PK profile in healthy subjects, and the observed PK parameters were close to those predicted based on the animal PK data. Mean C_{max} and AUC_{inf} values increased in an approximately dose-proportional manner in the studied dose range. Mean $t_{1/2}$ ranging from 21.8 to 29.2 days is consistent with the expected $t_{1/2}$ of human IgG4. Importantly, variations of the PK concentration and parameters (C_{max} and AUC_{inf}) of JNJ-64179375 were low, indicating PK predictability.

Consistent with the nonclinical findings, JNJ-64179375 produced a dose-dependent prolongation of the coagulation parameters (PT, aPTT, and TT) over the studied dose range. Based on fold-changes from baseline observed in this study, TT was the most sensitive assay for JNJ-64179375, which is consistent with its mechanism of action and direct effect on thrombin-mediated clot formation. The effect-time curves for all coagulation parameters seemed parallel to the plasma drug concentration-time curves of JNJ-64179375 with no apparent lag time.

1.1.2.3. Parts 2 and 3

Parts 2 and 3 of the study (1 single cohort in each part) had also completed dosing as of 21 April 2017. A blinded data review as of 02 May 2017 is briefly summarized below; however, this data was not included in the unblinded interim analysis as it was not available until after the cutoff date. Eight subjects were dosed intravenously with 1.0 mg/kg of JNJ-64179375 in Part 2 followed by either placebo (n=2) or 50 IU/kg of the 4-factor PCC Confidex® (n=6). Confidex did not appear to reverse the effects of JNJ-64179375 on either aPTT or TT. In Part 3, 8 subjects were dosed subcutaneously with either 1.0 mg/kg of JNJ-64179375 (n=6) or placebo (n=2). The PK data showed the expected delay to peak drug levels. For both cohorts, the bleeding adverse events were mostly mild skin-site events as observed in Part 1. One moderate intensity epistaxis bleeding event was reported in Part 2.

In the nonclinical studies, 4-factor PCC and activated PCC were able to normalize rat-tail bleeding times after the administration of JNJ-64179375 but did not reverse TT or aPTT prolongation (data on file). Therefore, the lack of reversal of TT and aPTT with 4-factor PCC in Part 2 of the Phase 1 study was not unexpected and likely reflects the insensitivity of these coagulation assays for measuring the potential hemostatic effects of PCC administration.

1.2. Comparator Drug

Eliquis® (apixaban)

The following information, taken from the European Union Summary of Product Characteristics, is intended to provide a brief, representative overview of apixaban.[8]

Eliquis® (apixaban) is a potent, oral, reversible, direct and highly selective active-site inhibitor of FXa. Apixaban does not require antithrombin III for antithrombotic activity. It inhibits free and clot-bound FXa and prothrombinase activity. Apixaban has no direct effects on platelet aggregation but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, apixaban prevents thrombin generation and thrombus development. Apixaban does not have any

effects on TT but does prolong PT and aPTT although the changes in these assays are small and variable at therapeutic doses.

Apixaban is indicated in the European Union for the prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery. For the prevention of VTE after TKR surgery, the recommended dose of apixaban is 2.5 mg taken orally twice daily, with the initial dose taken 12 to 24 hours after surgery. The recommended duration of treatment is 10 to 14 days.

The ADVANCE-1 and ADVANCE-2 studies included subjects who had undergone a TKR for one or both knees.

In the ADVANCE-1 study, which included 3,195 randomized subjects and 3,184 subjects in the safety population, apixaban 2.5 mg twice daily following TKR was compared with enoxaparin 30 mg twice daily. Both medications were started 12 to 24 hours after surgery and continued for 10 to 14 days. The primary efficacy endpoint was total VTE defined as the composite of adjudicated asymptomatic and symptomatic DVT, nonfatal PE, or all-cause death. The primary safety outcome was major bleeding during the treatment period or within 2 days after the last dose of the study drug. The total VTE rates were similar for apixaban and enoxaparin although statistically apixaban did not meet 1 of the 2 prespecified criteria for noninferior efficacy. Bleeding events were lower in the apixaban group.[23] (Table 4 and Table 5)

In the ADVANCE-2 study, which included 3,057 randomized subjects and 3,009 subjects in the safety population undergoing elective TKR surgery, subjects received either apixaban 2.5 mg given orally twice daily or enoxaparin 40 mg SQ once daily. Apixaban was started 12 to 24 hours after surgery, while enoxaparin was started 9 to 15 hours before surgery, with both drugs given for 10 to 14 days. The primary efficacy endpoint was total VTE and the primary safety outcome was major bleeding reported during the treatment period. Apixaban demonstrated a statistically superior reduction in total VTE and in the major VTE endpoint, a composite of proximal DVT, nonfatal PE, and VTE-related death, compared with enoxaparin. The safety endpoints of major bleeding, the composite of major and clinically relevant nonmajor bleeding, and all bleeding were not statistically different but were numerically lower for subjects treated with apixaban 2.5 mg twice daily compared with enoxaparin 40 mg SQ once daily.[24] (Table 4 and Table 5)

Table 4: ADVANCE-1 and ADVANCE-2 Safety Results

	Oral Apixaban 2.5 mg BID		SQ Enoxaparin 30 mg BID		Difference in Risk (95% CI)	p-value
ADVANCE-1	**N=1,596**	**95% CI**	**N=1,588**	**95% CI**		
Major Bleeding	11 (0.7)	0.4-1.3	22 (1.4)	0.9-2.1	-0.81 (-1.5 to 0.1)	0.05
CRNM	35 (2.2)	1.6-3.1	47 (3.0)	2.2-3.4	-0.77 (-1.8 to 0.3)	
Surgical site[†]	22 (1.4)		35 (2.2)			
Major or CRNM bleeding	46 (2.9)	2.2-3.8	68 (4.3)	3.4-5.4	-1.46 (-2.8 to 0.2)	0.03
All bleeding events	85 (5.3)	4.3-6.6	108 (6.8)	5.7-8.2	-1.52 (-3.2 to 0.1)	0.08
Minor bleeding events	39 (2.4)		40 (2.5)			

	Oral Apixaban 2.5 mg BID	SQ Enoxaparin 40 mg QD		
ADVANCE-2	**N=1,501**	**N=1,508**	Absolute Risk Difference	p-value
Major Bleeding	9 (0.6)	14 (0.9)	-0.3 (-1.0 to 0.3)	0.3
CRNM	44 (2.9)	58 (3.8)	-0.9 (-2.2 to 0.4)	0.17
Surgical site[†]	32 (2.1)	44 (2.9)		
Major + CRNM bleeding	53 (3.5)	72 (4.8)	-1.2 (-2.7 to 0.2)	0.09
All bleeding events	104 (6.9)	126 (8.4)	-1.4 (-3.3 to 0.5)	0.14
Minor bleeding events	51 (3.4)	54 (3.6)		

BID=twice daily; CI=confidence interval; CRNM=clinically relevant nonmajor; N=number; QD=once daily; SQ=subcutaneous
[†]Numbers are from investigator reports
Source: Lassen 2009[23]; Lassen 2010[24]

Table 5: ADVANCE-1 and ADVANCE-2 Efficacy Results

Intended Treatment Period	Oral Apixaban 2.5 mg BID		SQ Enoxaparin 30 mg BID		Relative Risk (95% CI)	Difference in Risk (95% CI)
ADVANCE-1	**n/N**	**95% CI**	**n/N**	**95% CI**		
Total VTE	104/1157	9.0 (7.47-10.79)	100/1130	8.8 (7.33-10.66)	1.02 (0.78-1.32)	0.11 (-2.22-2.44)
Major VTE	26/1269	2.0 (1.39-3.01)	20/1216	1.6 (1.06-2.55)	1.25 (0.70-2.23)	0.36 (-0.68-1.40)
Symptomatic VTE and VTE-related death	19/1599	1.2 (0.75-2.95)	13/1596	0.8 (0.46-1.41)	1.46 (0.72-2.95)	0.38 (-0.30-1.06)
All DVT	89/1142	7.8 (6.37-9.51)	92/1122	8.2 (6.73-9.97)	---	---
All PE	16/1599	1.0 0.61-1.64	7/1596	0.4 (0.20-0.93)	---	---

			SQ Enoxaparin 40 mg QD		Relative Risk (95% CI)/ p-value	Absolute risk difference (%)
ADVANCE-2	**n/N**	**Rate**	**n/N**	**Rate**		
Total VTE	147/976	15.0 (12.95-17.46)	243/997	24.37 (21.81-27.14)	0.62 (0.51-0.74)/ ≤0.0001	-9.27% (-12.74-[-5.79])
Major VTE	13/1195	1.09 (0.62-1.88)	26/1199	2.17 (1.47-3.18)	0.5 (0.26-0.97)/ 0.0186	-1.04% (-2.03-[-0.05])
Symptomatic VTE and VTE-related death	7/1528	0.46% (0.20 - 0.97)	7/1529	0.46 (0.20-0.97)	1.00 (0.35-2.85)/ ---	0.00% (-0.48-0.48)
All DVT	142/971	14.6% (12.5 - 17.0)	243/997	24.4 (21.8-27.1)	---/---	---
All PE	4/1528	0.26% (0.08 – 0.70)	0/1529	0.00 (0.00-0.31)	---/---	---

BID=twice daily; CI=confidence interval; DVT=deep vein thrombosis; n/N=number; PE=pulmonary embolism; QD=once daily; SQ=subcutaneous; VTE=venous thromboembolism
Source: Lassen 2009[23]; Lassen 2010[24]

1.3. Overall Rationale for the Study

Low molecular-weight heparins have a long and well-established role in the prevention of VTE in subjects undergoing TKR surgery, and while very effective with an acceptable bleeding risk, SQ dosing once or twice a day is required. More recently, several DOACs (eg, apixaban, rivaroxaban, dabigatran, edoxaban) have been approved for use in TKR, based on comparisons with the LMWH, enoxaparin, and their use has become more widespread in this patient population. Apixaban starting 12 to 24 hours after TKR surgery demonstrated superior efficacy compared with enoxaparin 40 mg once daily and similar efficacy to enoxaparin 30 mg twice daily, with numerically less bleeding than both enoxaparin regimens.[23,24] Apixaban was chosen as the active comparator for this study because it is orally administered and compares favorably with enoxaparin for both efficacy and bleeding endpoints.

JNJ-64179375 is a first-in-class, recombinant, fully human IgG4 monoclonal antibody that binds reversibly with high affinity and specificity to the exosite-1 region on thrombin. By only blocking exosite-1, the catalytic activity of the protease is maintained. Therefore, this unique

mechanism of action of JNJ-64179375 may offer the potential for noninferior (or superior) efficacy compared with currently available anticoagulant drugs (eg, vitamin K antagonists, enoxaparin, and DOACs) 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] As a monoclonal antibody, JNJ-64179375 has an expected duration of action of approximately 4 weeks, thereby allowing for the postoperative administration of a single IV dose to be used for VTE prophylaxis after TKR surgery. Based on the preclinical and Phase 1 studies conducted to date, JNJ-64179375 is anticipated to have a favorable safety profile with respect to bleeding risk. Therefore, JNJ-64179375 offers the potential for an efficacious treatment that has limited bleeding, with a simpler dosing regimen compared with currently available oral or parenteral treatments.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Part 1

In men and women undergoing primary unilateral TKR surgery, after single-ascending IV doses of JNJ-64179375 or 10 to 14 days of oral apixaban:

Primary Objective

The primary objective is to assess the safety and tolerability of JNJ-64179375 for each dose level for dose escalation within Part 1 and any bleeding events (the composite of major, clinically relevant nonmajor, and minimal bleeding events) for the selection of doses for Part 2.

Secondary Objectives

- To assess the dose response of JNJ-64179375 for the 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 event
- To assess the dose response of JNJ-64179375 for the prevention of total VTE (proximal and/or distal DVT [asymptomatic confirmed by venography assessment of the operated leg or objectively confirmed symptomatic], nonfatal PE, or any death) and the individual components of total VTE

Part 2

In men and women undergoing primary unilateral TKR surgery, after a single IV dose of JNJ-64179375 or 10 to 14 days of oral apixaban:

Primary Objective

The primary objective is to assess the efficacy dose response of JNJ-64179375 for the prevention of total VTE (proximal and/or distal DVT [asymptomatic confirmed by venography assessment of the operated leg or objectively confirmed symptomatic], nonfatal PE, or any death).

Key Secondary Objectives

- To assess the dose response of JNJ-64179375 for the 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 event
- To assess the dose response of JNJ-64179375 for the prevention of major VTE (asymptomatic confirmed by venography assessment of the operated leg or objectively confirmed symptomatic proximal DVT, nonfatal PE, or any death) and the individual components of the total VTE endpoint

Common Objectives in Parts 1 and 2

Other Secondary Objectives

- To assess the effect of individual doses of JNJ-64179375 compared with apixaban for both efficacy and safety endpoints, with the goal to identify a studied or model-predicted dose with the most promising benefit-risk profile for a more extensive evaluation in Phase 3
- To assess the effect of JNJ-64179375 compared with apixaban on wound or joint complications in the operated leg

Exploratory Objectives

- To assess the effect of JNJ-64179375 compared with apixaban on other thrombotic events (ie, myocardial infarction [MI], ischemic stroke, peripheral arterial embolism)
- To evaluate the cost effectiveness of JNJ-64179375 compared with apixaban based on health resource utilization
- To assess the PK, PD, and PK/PD relationships of JNJ-64179375 in men and women undergoing primary unilateral TKR surgery and the relation of these measures to efficacy and safety endpoints (eg, exposure-response analyses)
- To evaluate the PD assays (TT, ECT, PT, aPTT, and D-dimer) to determine the most appropriate tests to measure the effect of JNJ-64179375

2.1.2. Endpoints

The endpoints of the study will be the same for Parts 1 and 2 although the focus of Part 1 will be primarily dose escalation based on safety while the focus of Part 2 will primarily be the assessment of dose response in both safety and efficacy.

Common Endpoints in Parts 1 and 2

Primary Safety Endpoint

The primary safety endpoint is any bleeding event defined as the composite of major, clinically relevant nonmajor, and minimal bleeding events assessed through the Day 10-14 visit.

Primary Efficacy Endpoint

The primary efficacy endpoint is total VTE, defined as the composite of proximal and/or distal DVT (asymptomatic confirmed by venography assessment of the operated leg or objectively confirmed symptomatic), nonfatal PE, or any death assessed through the Day 10-14 visit.

Key Secondary Endpoints

The key secondary endpoints are the assessment of the primary endpoints through the Week 18 visit, and:

- All individual components of the primary safety endpoint (major bleeding, clinically relevant nonmajor bleeding, and minimal bleeding)
- Composite of major and clinically relevant nonmajor bleeding
- Major VTE, a composite of proximal DVT (asymptomatic confirmed by venography assessment of the operated leg or objectively confirmed symptomatic), nonfatal PE, or any death
- All individual components of the primary efficacy endpoint (ie, proximal and/or distal DVT [asymptomatic confirmed by venography assessment of the operated leg or objectively confirmed symptomatic], nonfatal PE, any death)

Other Secondary Endpoints

- Any wound or joint complication in the operated leg

Exploratory Endpoints

- Other thrombotic events (ie, MI, ischemic stroke, peripheral arterial embolism)
- The total length of the initial hospitalization, including the level of care and discharge destination
- The incidence of rehospitalization for any reason
- The number of scheduled and unscheduled visits, including the associated cost to healthcare providers for study outcomes, any other medical reasons, and the diagnostic procedures used in relation to study endpoints
- Calculation of PK parameters, eg, CL, volume of distribution (Vd), $t_{1/2,}$ AUC_{inf}, and C_{max}
- Changes in PD by dose: TT, ECT, PT, aPTT, and D-dimer
- Changes in PD assays as listed above by concentration metrics (AUC_{inf}, C_{max}, or time-matched concentrations)

Refer to Section 9, Study Evaluations for evaluations related to endpoints.

2.2. Hypothesis

In Part 1, a range of doses of JNJ-64179375 will be assessed to determine if it is sufficiently safe to proceed with Part 2 of the study. No formal hypothesis testing will be conducted for Part 1. In Part 2, the clinical hypothesis is to demonstrate proof-of-efficacy based on the total VTE endpoint. This can be achieved by either showing that JNJ-64179375 has a statistically significant dose-response trend with respect to the total VTE endpoint, or the combined dose groups of JNJ-64179375 have a total VTE event rate of less than 30%.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, double-blind, double-dummy, active-controlled, multicenter, dose-escalation and dose-response study of JNJ-64179375. The study has 2 parts, dose-escalation and dose-response evaluation, and will be conducted in subjects undergoing primary unilateral elective TKR surgery. Part 1 will assess the safety of single-ascending IV doses of JNJ-64179375 while Part 2 will confirm the safety of the doses selected from Part 1 and will assess the efficacy dose-response relationship with respect to the selected doses in the parallel groups. Subjects will be men or women of non-childbearing potential ≥50 years of age, considered medically appropriate for postoperative anticoagulant prophylaxis based on the study- and local standard-of-care-required assessments for pre- and postoperative evaluation. Subjects will participate in either Part 1 or Part 2 of the study only. A total of approximately 1,500 subjects combined for Parts 1 and 2 are planned to be enrolled. Part 1 will include approximately 300 subjects and Part 2 will include approximately 1,200 subjects as described in Section 3.1.1, Part 1: Single-Ascending Dose and Section 3.1.2, Part 2: Dose-Response Confirmation, respectively.

For each subject in each part, the study will be conducted in 3 phases: an up to 30-day screening phase before surgery, a 14-day double-blind dosing phase, and a 16-week 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 the subject's participation in Part 1 or Part 2 after randomization will be approximately 18 weeks.

Screening for eligible subjects in Parts 1 and 2 may be done up to 30 days before randomization, pre- or postoperatively. Following primary unilateral elective TKR surgery, eligible subjects will be randomly assigned to treatment with either JNJ-64179375 or apixaban. All subjects will receive a single IV infusion of JNJ-64179375 or JNJ-64179375 placebo and oral apixaban or matching apixaban placebo the day after TKR surgery (Day 1, 0 hours), while the subject is still hospitalized and within 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. Details regarding the timing of oral dosing in relation to the start of the IV infusion are provided in Section 6, Dosage and Administration.

Following discharge or transfer to an alternate facility, subjects in both parts will be reminded to continue to take apixaban or matching apixaban placebo twice daily to complete a total of 10 to 14 days of dosing as described in Section 6, Dosage and Administration. Unilateral

venography assessment of the operated leg will be performed after the last dose of apixaban or matching apixaban placebo is taken as described in Section 9.2.1, Assessments for DVT.

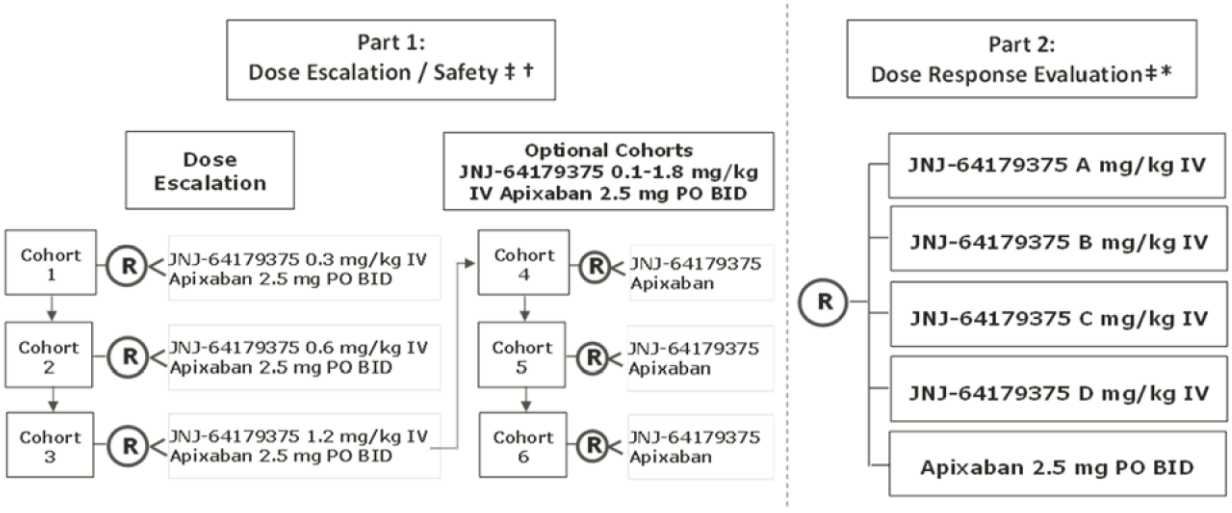
Subjects in both Parts 1 and 2 will return to the site for study-related procedures 5, 10, and 18 weeks after TKR surgery as described in the Time and Events Schedule that follows the Synopsis. Safety evaluations will include the monitoring of all nonserious and serious adverse events, (including adverse events of special interest: bleeding events, infusion reactions, hypersensitivity reactions, and wound or joint complications), clinical laboratory tests (ie, hematology, clinical chemistry, urinalysis), vital signs measurements (blood pressure, pulse/HR, temperature), and physical examinations. Pharmacokinetics (dense and sparse), PD, and immunogenicity samples will be collected and health resource utilization will also be assessed at the time points indicated in the Time and Event Schedule.

An Operations Committee (OC), Independent Data Monitoring Committee (IDMC), Steering Committee (SC), and independent Clinical Events Committee (CEC) will be commissioned for this study. Refer to Section 11.11, Committees.

An unblinded data review is planned for Part 1 after all subjects are expected to have completed the Day 10-14 visit to determine the dose range and doses of JNJ-64179375 for Part 2. Two planned, unblinded interim analysis will be conducted in Part 2 by the IDMC as part of the adaptive approach that will be used to guide decisions to drop and/or add doses of JNJ-64179375 and adjust the randomization ratio based on the available efficacy, safety, PK, and PD data. Additional details are provided in Section 11.10, Interim Analyses. An unblinded administrative interim analysis is planned after all subjects are expected to have completed the Day 10-14 visit in Part 2 to facilitate additional study planning as described in Section 11.10, Interim Analyses.

A diagram of the study design is provided below.

Schematic Overview of the Study



‡ Double-dummy design: Subjects in both parts will receive a single dose of IV JNJ-64179375 or JNJ-64179375 placebo and 10 to 14 days of apixaban or apixaban placebo PO BID, followed by unilateral venography and follow-up study visits through Week 18. Unique subjects will be enrolled in each part and within each part unique subjects will be enrolled in each cohort.

† Six cohorts of up to approximately 50 unique subjects per cohort (total of up to approximately 300 unique subjects) are planned but the number of cohorts and the size of each cohort may be adjusted based on the ongoing unblinded data review by the Operations Committee.

* The dose range and doses of JNJ-64179375 for Part 2 selected will be determined by a review of the data from Part 1.

BID = twice daily; IV = intravenous; PO = by mouth

3.1.1. Part 1: Single-Ascending Dose

Eligible subjects in Part 1 will be randomly assigned to a single-ascending IV dose of JNJ-64179375 or apixaban 2.5 mg given orally twice daily for 10 to 14 days. Six cohorts of up to approximately 50 unique subjects per cohort (total of up to approximately 300 unique subjects) are planned but the number of cohorts and the size of each cohort may be adjusted based on the ongoing unblinded data review by the OC. Within each cohort, subjects will be randomized in a 4:1 ratio to JNJ-64179375 or apixaban, respectively (ie, approximately 40 subjects to JNJ-64179375: approximately 10 subjects to apixaban). JNJ-64179375 will be administered in a dose-escalation manner, with planned doses of 0.3, 0.6, and 1.2 mg/kg in Cohorts 1, 2, and 3, respectively. In Part 1, the OC will be responsible for reviewing ongoing safety and efficacy data by unblinded subject treatment assignments approximately every 1 to 3 weeks. Subjects enrolled in the 3 optional cohorts will receive doses of JNJ-64179375 in the range of 0.1 to 1.8 mg/kg, which will be dependent on the available preliminary safety, tolerability, efficacy, PK, and PD data obtained from the preceding cohorts (refer to Section 6, Dosage and Administration for additional details). After all of the subjects in Part 1 are expected to have completed the Day 10-14 visit, an unblinded data review will be conducted by the OC, SC, IDMC, and sponsor to determine the dose range and doses for Part 2.

3.1.2. Part 2: Dose-Response Evaluation

Part 2 of this study has an adaptive design, with the intent to optimize data collection for the dose-response evaluation using multiple comparison procedure and modeling (MCP-Mod). Eligible subjects prior to the first interim analysis in Part 2 will be randomly assigned equally to 1 of up to 5 parallel treatment groups, including up to 4 dose levels of JNJ-64179375, given as a

single, active IV infusion, or oral apixaban 2.5 mg twice daily for 10 to 14 days. The number of doses and randomization ratio after the 2 interim analyses will depend on the interim analysis results. However, the number of ongoing doses of JNJ-64179375 in the study is not expected to exceed 4 doses. The Part 2 sample size is estimated to be 1,200 subjects. In Part 2, the IDMC will be responsible for monitoring ongoing safety and efficacy and for conducting the 2 planned interim analyses to apply the adaptive design rules. Subjects will be randomized to 1 of the treatment groups with a balanced randomization ratio until the first interim analysis. After the review of each planned interim analysis, the IDMC will make a recommendation to declare futility, adjust the study drug doses, or modify the randomization ratio (see Section 11.10, Interim Analyses for details). The SC and sponsor will make a decision whether to implement the IDMC's recommendation. The interim analyses will be performed after approximately 400 and 800 subjects are enrolled and are expected to have completed the Day 10-14 visit. The final number of subjects in each dose group will depend on the results of the interim analyses.

3.2. Study Design Rationale

Blinding, Control, Study Phase/Periods, Treatment Groups

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

The treatment phase duration of up to 14 days is the approved duration of therapy with apixaban after TKR surgery. JNJ-64179375 has an estimated human plasma $t_{½}$ of approximately 25 days based on preliminary data in healthy subjects. The 16-week follow-up duration (18 weeks from dosing) in this study is approximately 5 times the calculated $t_{1/2}$ of JNJ-64179375, and is therefore adequate for PK analysis and is consistent with the safety reporting period.

The dose-escalation design in Part 1 will allow for a careful stepwise approach to assess bleeding risk in subjects undergoing TKR surgery to determine the dose range for the parallel design in Part 2, which will confirm the safety and efficacy dose response of JNJ-64179375.

Study Population

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.[10,19] Over the past 20 years, Phase 2 studies of injectable anticoagulants (LMWH, fondaparinux) and all of the newer oral anticoagulants (apixaban, rivaroxaban, dabigatran, and edoxaban) were conducted in this population using venography to detect asymptomatic DVT. Subsequently, all of these oral medications were evaluated in large, similarly designed Phase 3 studies and have been approved by regulatory agencies for the prevention of VTE in TKR surgery because they were found to be at least as effective as LMWH, have a similar or improved bleeding profile, and have the convenience of

easy administration.[9,13,15,23,24,30] Therefore, the TKR study population is appropriate to evaluate the efficacy and safety of JNJ-64179375.

Total knee replacement surgery is most commonly performed due to arthritic disease of the joint, which occurs primarily in older men and women. The risks of VTE and bleeding also increase with age. Therefore, the intended population, which includes both men and women who are at least 50 years of age, is also appropriate. Women of childbearing potential are excluded from this study because reproductive toxicology testing of JNJ-64179375 has not been conducted.

Dose Selection

The Part 1 planned doses of JNJ-64179375 (0.3, 0.6, or 1.2 mg/kg) were chosen based on preclinical data and data from the Phase 1 study in healthy subjects (Protocol 64179375EDI1001). In preclinical venous thrombosis models in both rats and monkeys, JNJ-64179375 at a dose of 0.3 mg/kg demonstrated good efficacy, which increased even further at 1 mg/kg. In healthy subjects, the 0.3-mg/kg dose was associated with a maximum mean blood level of approximately 7 μg/mL and TT prolongation of approximately 3-fold from baseline while the 1-mg/kg dose had maximum mean blood levels of about 30 μg/mL, with TT prolongations of greater than approximately 5-fold from baseline. Both doses demonstrated an acceptable safety profile. Therefore, the starting dose of 0.3 mg/kg was selected as it should be effective for VTE prevention after TKR surgery and provides a wide safety margin from the Phase 1 doses that showed a bleeding signal (2.125 and 2.5 mg/kg). Dose escalation will then be guided by the OC based on accumulating data for both safety and efficacy. The highest planned dose in Part 1 of 1.2 mg/kg has been selected because it is similar to the 1-mg/kg dose studied in the Phase 1 study and is approximately 50% of the lowest dose with a bleeding signal (ie, 2.125 mg/kg) in healthy subjects. If the 0.3-mg/kg dose appears to be fully effective in Part 1, there is the option to study a lower dose (as low as 0.1 mg/kg); likewise, if the 1.2-mg/kg dose appears well tolerated and incremental benefit is expected from a higher dose, there is the option to study a higher dose (up to 1.8 mg/kg). The dose selection in Part 2 will be based on the safety and efficacy results/comprehensive analyses from Part 1, with the goal being to study the widest possible dose range supported by the data.

Choice of Comparator

An active control (apixaban) will be used because pharmacologic VTE prophylaxis is considered standard-of-care in subjects undergoing TKR surgery. Given that VTE and bleeding event rates vary across studies, the active control will also provide an internal reference for comparison with JNJ-64179375 in this study.

Apixaban was chosen as the comparator in this study because it is an approved oral drug for this indication, has a start time after surgery that is preferred by many surgeons, and has demonstrated favorable efficacy and safety (ie, bleeding) results compared with enoxaparin. Refer to Section 1.2, Comparator Drug for additional details regarding apixaban.

The 2.5-mg dose of apixaban, taken twice daily for 10 to 14 days beginning 12 to 24 hours after the end of TKR surgery will be used in this study as it is the approved dosage regimen (in approved countries) for the indication being studied.[8]

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 bleeding events 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 the approved duration of therapy for apixaban.

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%).[20] However, ultrasound has repeatedly been shown to have very low sensitivity compared with venography for detecting asymptomatic DVT in the postoperative setting.[20,27] In a meta-analysis of 15 studies, the sensitivity of ultrasound compared with venography for detecting asymptomatic DVT was 47%.[20] 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% confidence interval [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.[27]

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 the 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.[5,22,31] Venography produces plausible and reliable results in clinical studies[7,14,29] 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.[11,13] However, as unilateral venography of the operated leg detects over 90% of DVTs after TKR surgery[12] and exposes subjects to less risk (radiation, contrast dye, venipuncture) and less discomfort, only venography of the operated leg will be performed in this study.

Suspected symptomatic efficacy (thrombotic) events (ie, DVT, PE, death, MI, stroke, peripheral arterial embolism) will also be specifically assessed in this study as these are clinically important events from the perspective of both the subject and the surgeon.

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.[21] Published guidelines that describe how to define major bleeding events after major orthopedic surgery will be followed.[28] For nonmajor bleeding events, standardized definitions, as utilized in the Phase 3 studies of apixaban, will be followed.[23,24] 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 and Immunogenicity Measures

Pharmacokinetic blood samples will be collected from all subjects and analyzed for subjects who are randomly assigned to treatment with JNJ-64179375 to further understand the PK characteristics and variability of JNJ-64179375 in the TKR patient population. The combination of dense and sparse PK samples in this patient population will be sufficient for the development of a population PK model and predicted concentrations from such a model will allow for the development of exposure-response models for various endpoints related to safety and efficacy. Immunogenicity blood samples will be collected from all subjects and analyzed for subjects randomly assigned to JNJ-64179375 to assess for the development of any ADAs.

Choice of Pharmacodynamic/Biomarker and PK/PD

The PD assays (TT, ECT, PT, aPTT, and D-dimer) will be used to evaluate the mechanism of action and pharmacologic activity of JNJ-64179375. A battery of coagulation assays with different inhibition profiles for JNJ-64179375 has been chosen to evaluate those assays that might be most appropriate for assessing both pharmacologic activity and any relationships with PK and/or efficacy and/or safety endpoints. The goal of the PD analyses is to evaluate the PD effects of JNJ-64179375, the PK/PD relationship, and PD outcome relationships. Additional details regarding the collection of the PD assessment blood samples and the test procedures will be included in the laboratory manuals. It is expected that apixaban will have no effect or minimal effects on all of the coagulation assays and therefore, analysis of the apixaban samples is not planned.

Biomarker samples may be used to help address emerging issues and enable the development of safer, more effective, and ultimately individualized therapies. An exploratory objective will be to

evaluate and compare the performance of the various PD assays. A central specialty laboratory will be used to provide more robust quality control for these assays by performing them in batches and to maintain the study blind. No local PD sample collection is planned. Detailed descriptions of each of the assays are provided in Section 9.4, Pharmacodynamic/Biomarker Evaluations.

Choice of Health Resource Utilization Data Collection

With the growing demand on limited healthcare resources and concern about healthcare expenditures, the collection of health resource utilization data will be integrated into the study. Health resource utilization endpoints collected from this study will be key inputs for conducting exploratory cost-effectiveness analyses.

4. SUBJECT POPULATION

It is estimated that approximately 1,500 subjects will be randomly assigned to treatment in this study as described in Section 3.1.1, Part 1: Single-Ascending Dose and Section 3.1.2, Part 2: Dose-Response Evaluation. Subjects who are withdrawn early from the study will not be replaced. For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

Screening for eligible subjects in Parts 1 and 2 may be done up to 30 days before randomization, pre- or postoperatively. 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.

4.1. Inclusion Criteria

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

1. Male or female of non-childbearing potential

2. At least 50 years of age or older

3. Weight ≥40 kg to ≤150 kg

4. Medically appropriate for postoperative anticoagulant prophylaxis as determined by the investigator on the basis of the physical examination, medical history, and vital signs measurements performed as part of screening for elective TKR surgery and any examinations performed as part of standard postoperative care following surgery

5. Medically appropriate for postoperative anticoagulant prophylaxis on the basis of clinical laboratory tests performed as part of screening for elective TKR surgery and any examinations performed as part of standard postoperative care following surgery. If the results of the 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.

6. Has undergone an elective primary unilateral TKR

7. 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.

8. Before randomization, a woman must not be of childbearing potential defined as:

    - 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.

    If reproductive status is questionable, additional evaluation should be considered in consultation with the sponsor.

9. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study

10. Contraceptive use by men should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies.

    During the study from Day 1 through the Week 18 visit, a man

    - Who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository)
    - Who is sexually active with a woman who is pregnant must use a condom
    - Must agree not to donate sperm
    - Must agree not to father a child

11. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.2. Exclusion Criteria

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

1. Any condition for which the use of apixaban is not recommended in the opinion of the investigator (eg, spinal anesthesia procedure with bleeding or significant trauma, postoperative epidural analgesia with an epidural catheter within 5 hours of oral or IV study drug administration, previous allergic reaction, creatinine clearance <15 mL/minute or on dialysis)

2. Bilateral, revision or unicompartmental procedure

3. Known or suspected hypersensitivity or intolerance to any biologic medication or known allergies or clinically significant reactions to murine, chimeric, or human proteins, monoclonal antibodies or antibody fragments, or any of the excipients of JNJ-64179375 (refer to Investigator's Brochure)[17]

4. 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)

5. Known previous DVT in either lower extremity

6. Chronic anticoagulation therapy for any condition (eg, atrial fibrillation, mechanical heart valve) is required

7. Any preplanned invasive procedure (eg, surgery, colonoscopy) up to Week 18 for which anticoagulant or antiplatelet therapy would be interrupted

8. Planned use of intermittent pneumatic compression after randomization

9. Received an investigational drug (including investigational vaccines, experimental antibody or biologic therapy) within the previous 6 months or 5 half-lives, whichever is longer, or received any other experimental therapy, 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

10. Previous randomized subject in this study or participated in previous studies with JNJ-64179375

11. 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

12. 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

13. 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, or 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 the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 9.1.2, Screening Phase, describes options for retesting. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation. Additionally, for apixaban, investigators should follow the prohibitions and restrictions in the Summary of Product Characteristics.

1. Refer to Section 8, Prestudy and 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 Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria.

3. A man who is sexually active must agree to use a barrier method of contraception method as described in Section 4.1, Inclusion Criteria. All men must also not donate sperm through the Week 18 visit.

4. Subjects who are given permission by the treating physician to resume normal activity following TKR surgery should avoid activities that could produce significant trauma, and when participating in low-risk sports (eg, biking), proper safety gear (eg, helmet, gloves) should be worn through the Week 18 visit. In addition, subjects should be more cautious when using sharp objects (eg, razors, scissors, and knives) through the Week 18 visit.

5. Subjects should not donate blood or blood products for the duration of the study and for at least 4 weeks after the Week 18 visit.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. In Part 1, within each of the up to 6 planned cohorts, subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and in Part 2 will also be stratified by region. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

In Part 2, subjects will be randomly assigned to 1 of the treatment groups based on a computer-generated randomization schedule as previously described for Part 1. Separate randomization schedules will be used for Part 1 and Part 2 of the study.

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 blind for an individual subject.

Data that may potentially unblind the treatment assignment (ie, coagulation testing, study drug concentrations, antibodies to JNJ-64179375, study drug preparation/accountability data, treatment allocation, 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 the investigators, 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 coagulation assays locally unless considered necessary for subject 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.

Under normal circumstances, the 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 identity 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 the 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 who have had their treatment assignment unblinded may continue on study drug unless the subject meets a study drug discontinuation criterion. Investigators should not disclose the treatment assignment to the subject whenever possible, even in a special situation where the treatment assignment has been unblinded to the investigator. Subjects who have had their treatment 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, the randomization codes and 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 in Part 1 and of the IDMC for data reviews and interim analyses in Part 2. Refer to Section 11.10, Interim Analysis, Section 11.11.1, Operations Committee, and Section 11.11.2, Independent Data Monitoring Committee for additional details.

JNJ-64179375 (Parts 1 and 2)

Using the randomization code, an unblinded pharmacist or other appropriately licensed and authorized health professional at each study site will prepare an individual study drug dose of JNJ-64179375 or JNJ-64179375 placebo (0.9% normal saline) for each subject in a 50-mL normal saline IV bag as per the directions in the Investigational Product Preparation Instructions (IPPI). Subjects randomized to apixaban will receive a 0.9% normal saline IV bag with no active study drug. All study drugs will have a blinded label applied prior to dispensing.

Apixaban (Parts 1 and 2)

Using the randomization code, the pharmacist or other appropriately licensed and authorized health professional will dispense a bottle of blinded oral study drug (over-encapsulated apixaban tablets or matching apixaban placebo capsules) to each subject at the time of randomization. The subject will be administered the capsules from the bottle while hospitalized and will be given the bottle for outpatient use at the time of discharge from the hospital. Refer to Section 6, Dosage and Administration for additional details regarding subject dosing.

6. DOSAGE AND ADMINISTRATION

In both Parts 1 and 2, subjects will be randomly assigned to receive an active single IV dose of JNJ-64179375 or apixaban 2.5 mg given orally twice daily for 10 to 14 days. The administration of the study drugs will begin the day after the TKR surgery (Day 1, 0 hours), while the subject is still hospitalized and within 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. Within that timeframe, both the single IV infusion and the oral study drug should be administered as close as possible to each other,

with up to a maximum of 60 minutes between the start of the IV infusion and the first dose of the oral study drug. Subjects will be randomly assigned to the treatment groups as follows:

Part 1

- Cohort 1: JNJ-64179375 0.3 mg/kg IV/JNJ-64179375 placebo (saline) IV infusion and matching apixaban placebo/apixaban, orally twice a day for 10 to 14 days
- Cohort 2: JNJ-64179375 0.6 mg/kg IV/JNJ-64179375 placebo (saline) IV infusion and matching apixaban placebo/apixaban, orally twice a day for 10 to 14 days
- Cohort 3: JNJ-64179375 1.2 mg/kg IV/JNJ-64179375 placebo (saline) IV infusion and matching apixaban placebo/apixaban, orally twice a day for 10 to 14 days

Optional Cohorts (JNJ-64179375 in the Range of 0.1 to 1.8 mg/kg)

The doses of JNJ-64179375 to be used in the optional cohorts will be dependent on the available preliminary safety, tolerability, efficacy, PK, and PD data obtained from the preceding cohorts as described in Section 3.1.1, Part 1, Single-Ascending Dose. Doses within the optional cohorts will either be new doses within the range of 0.1 to 1.8 mg/kg not previously administered in the preceding cohorts, or doses from the preceding cohorts, which may be repeated, as needed.

- Cohort 4: JNJ-64179375 Dose to be determined (TBD) mg/kg IV/JNJ-64179375 placebo (saline) IV infusion and matching apixaban placebo/apixaban, orally twice a day for 10 to 14 days
- Cohort 5: JNJ-64179375 Dose TBD mg/kg IV/JNJ-64179375 placebo (saline) IV infusion and matching apixaban placebo/apixaban, orally twice a day for 10 to 14 days
- Cohort 6: JNJ-64179375 Dose TBD mg/kg IV/JNJ-64179375 placebo (saline) IV infusion and matching apixaban placebo/apixaban, orally twice a day for 10 to 14 days

Part 2

- Group A: JNJ-64179375 Dose A mg/kg IV and apixaban placebo orally twice a day for 10 to 14 days
- Group B: JNJ-64179375 Dose B mg/kg IV and apixaban placebo orally twice a day for 10 to 14 days
- Group C: JNJ-64179375 Dose C mg/kg IV and apixaban placebo orally twice a day for 10 to 14 days
- Group D: JNJ-64179375 Dose D mg/kg IV and apixaban placebo orally twice a day for 10 to 14 days
- Group E: JNJ-64179375 placebo (saline) IV and apixaban 2.5 mg orally twice a day for 10 to 14 days

Doses of JNJ-64179375 may change after the interim analyses in Part 2 as described in Section 11.10, Interim Analyses.

For both parts, JNJ-64179375 will be prepared according to the subject's weight and treatment assignment by the pharmacist or other appropriately licensed and authorized health professional

who is not blinded to the treatment assignment. All study drug administrations of JNJ-64179375 must be calculated based on the subject's weight on Day -1 or prior to dosing on Day 1. The single infusion of JNJ-64179375 or JNJ-64179375 placebo (saline) will be administered under the supervision of the investigator or his/her designee over a period of approximately 30 minutes by infusion pump or by gravity flow using a flow regulator. A physician must be immediately available at the study site at all times during the administration of the study drug infusion. Detailed instructions for dose preparation, dosing procedures, and storage conditions of the study drug will be provided to the study site in the IPPI. These documents may be revised as needed and should be maintained in the study files.

The first dose of apixaban or matching apixaban placebo will be administered as previously described. Subjects will receive apixaban or matching apixaban placebo twice a day while hospitalized and will be given a supply of apixaban or matching apixaban placebo at the time of discharge or transfer to an alternate facility, with instructions to take the study drug orally, twice a day at approximately the same times each day to complete a total of 10 to 14 days of dosing. Apixaban or matching apixaban placebo should be swallowed with water, with or without food.

If a dose of apixaban or matching apixaban placebo is missed, the missed dose should be taken as soon as possible and then the subject should continue with the twice-daily intake as previously instructed. The dose should not be doubled to make up for a missed dose and more than 2 doses should not be taken on the same day.

Refer to Section 14, Study Drug Information for details regarding a physical description of the study drugs, packaging, labeling, and preparation, handling, and storage.

7. TREATMENT COMPLIANCE

Drug supplies will be inventoried and accounted for throughout the study. The IWRS will track the study drug dispensed to (JNJ-64179375 or apixaban/matching apixaban placebo) and returned by (apixaban or matching apixaban placebo only) subjects.

JNJ-64179375 or JNJ-64179375 placebo will be administered as a single IV infusion by qualified study site personnel and the details of the administration will be recorded. For apixaban or matching apixaban placebo, subjects will be required to return empty study drug containers and unused study drug at their Day 10-14 visit, at which time study drug accountability will be performed.

8. PRESTUDY AND CONCOMITANT THERAPY

Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

The use of the following medications/therapies is not permitted from randomization through Week 18:

- Additional anticoagulant(s) (eg, vitamin K antagonists, Factor IIa or FXa inhibitors). The blinded study drug (apixaban) will be discontinued in subjects who develop any condition that requires long-term anticoagulation (eg, DVT, atrial fibrillation). Refer to Section 9.2, Efficacy Evaluations for details regarding the management approach for subjects who develop a symptomatic VTE event or who have asymptomatic DVT detected by venography.
- Antiplatelet therapies (eg, platelet adenosine diphosphate $P2Y_{12}$ receptor antagonist [eg, clopidogrel, ticagrelor]) during the study except for aspirin ≤100 mg/day
- Nonsteroidal anti-inflammatory drugs (NSAIDs) 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.
- Intermittent pneumatic compression after randomization (all other mechanical VTE prevention methods such as foot pumps, graduated compression stockings and continuous passive motion devices are permitted)

In addition, the use of the following medications is not permitted concomitantly with apixaban or matching apixaban placebo:

- Concomitant systemic treatment with strong inhibitors of both cytochrome P450 (CYP) 3A4 and P-glycoprotein (P-gp), such as azole-antimycotics (eg, ketoconazole, itraconazole, voriconazole, and posaconazole) and human immunodeficiency virus protease inhibitors (eg, ritonavir). These medicinal products may increase apixaban exposure by 2-fold or greater in the presence of additional factors that increase apixaban exposure (eg, severe renal impairment).[8]
- Strong CYP3A4 and P-gp inducers (eg, rifampicin, phenytoin, carbamazepine, phenobarbital, or St. John's Wort). The concomitant use with apixaban may lead to an approximately 50% reduction in apixaban exposure.[8]

Only selected medications administered up to 7 days before randomization will be recorded in the electronic case report form (eCRF) as prestudy therapies (eg, TXA, antiplatelet therapies, anticoagulant therapies, and NSAIDs).

All concomitant pharmacologic therapies, including prescription or over-the-counter medications, products to manage bleeding, vaccines, vitamins, and herbal supplements different from the study drug must be recorded throughout the study from the time of randomization through the last follow-up visit on Week 18.

All non-pharmacologic therapies such as intermittent pneumatic compression devices, foot pump devices, continuous passive motion devices, compression stockings, electrical stimulation, acupuncture, special diets, exercise regimens, including physical and occupational therapy 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 its indication.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, PK, immunogenicity, PD/biomarker, health resource utilization, and safety measurements applicable to this study. The Time and Events Schedule, and the description of the study phases that follows, are applicable to subjects participating in either Part 1 or Part 2 of the study, unless otherwise noted.

If multiple assessments are scheduled for the same time point, it is recommended that procedures be performed in the following order: ECG (as applicable), vital signs, and blood draw.

Blood collections for PK and PD assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified time points, if needed. Actual dates and times of assessments will be recorded in the source documentation. Blood samples for PK and PD assessments on Day 1 postdose should be collected in the opposite arm as the infusion of JNJ-64179375 or placebo. Blood samples will be collected in the following order: safety (serum chemistry, hematology), PK, immunogenicity, and PD.

Venous blood will be collected for all blood-based analysis. Blood will be drawn using a cannula or by venipuncture. Only saline (not heparin) can be used for flushing the cannula. If blood samples are collected via an indwelling cannula, an appropriate amount (ie, 1 mL) of fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before blood samples are taken.

The total blood volume to be collected from each subject will be approximately 95.4 mL for subjects with dense PK sampling and approximately 80.4 mL for subjects with sparse PK sampling as described in Table 6. It is important to record the exact date and time for PK sample collection even if the time deviates slightly from the scheduled time of collection.

Table 6: Volume of Blood to be Collected From Each Subject

Type of Sample	Volume per Sample (mL)[a]	No. of Samples per Subject	Approximate Total Volume of Blood (mL)[b,c]
Safety (including follow-up assessments)			
Hematology	2.0	5	10.0
Serum chemistry	2.5	5	12.5
PK samples, including ADA, where required			
Dense	5.0	9	45.0
Sparse	5.0	6	30.0
PD/Biomarker samples			
TT, PT, aPTT	4.5	4	18.0
ECT (alone)	1.8	1	1.8
ECT including D-dimer	2.7	3	8.1
Approximate Total[c] for Dense PK subjects			95.4
Approximate Total[c] for Sparse PK subjects			80.4

ADA=antidrug antibody; aPTT=activated partial thromboplastin time; ECT=ecarin clotting time; No.=number; PD = pharmacodynamics; PK=pharmacokinetic, PT = prothrombin time; TT = thrombin time

[a] Some sample volumes will vary slightly for subjects in Japan (due to customs requirements for laboratory tubes).

[b] Calculated as number of samples per subject multiplied by volume of blood per sample.

[c] Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

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

Additional blood samples may be collected, if necessary, for additional safety, PK, or PD assessments based on emerging data, but the total blood volume collected from an individual subject during 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.

Health resource utilization data will be collected. Refer to Section 9.6, Health Resource Utilization for details.

9.1.2. Screening Phase

The screening phase will occur up to 30 days before randomization, pre- or postoperatively. Potential subjects may be evaluated for eligibility before or after their unilateral elective TKR surgery. Final eligibility must be confirmed after surgery, prior to randomization.

Prior to conducting any study-related procedure, the investigator (or designated study personnel) will review and explain the written ICF to each subject. No study procedures can be performed until the subject signs the ICF. At the time of informed consent, 2 alternative means of contact for the each subject will be collected (eg, contact information of the subject's children, spouse, significant other, caretaker, legal representative, or health care professional). 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, and use of all mechanical VTE prophylaxis methods) will be collected in the eCRF. In addition, the subject will respond to questions (see Attachment 1) regarding his or her family and personal bleeding history, including any bleeding from previous surgical procedures.

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.

9.1.3. Double-Blind Dosing Phase

Day 1/Day of Randomization

On Day 1, subjects who meet all of the eligibility criteria will be randomly assigned to study drug, either JNJ-64179375 or apixaban as described in Section 6, Dosage and Administration. JNJ-64179375 or JNJ-64179375 placebo will be administered under the supervision of the investigator or his/her designee. Subjects will also begin to take oral apixaban or matching apixaban placebo twice daily. All procedures specified for the 0-hour time point should be conducted prior to the first dose of the study drug. The postdose samples will be drawn at 1 hour (±10 minutes) and 4 hours from the start of the IV infusion.

Dosing Visits

Subjects will be discharged from the hospital or transferred to an alternate facility at an appropriate time as determined by the managing physician. The Day 2 blood sample will be drawn 24 hours after the start of the IV infusion and may be done with the subject as an inpatient or outpatient. Study procedures will be conducted on Days 3 (48 hours) and 7 (144 hours) only for those subjects who are still hospitalized. At the time of hospital discharge or transfer to an alternate facility, the subject will be reminded to continue to take the oral apixaban or matching apixaban placebo twice daily to complete a total of 10 to 14 days of dosing, the duration of which will be determined by the managing physician. Subjects who complete dosing with apixaban or matching apixaban placebo will return to the study site for final assessments in the double-blind dosing phase (Day 10-14 visit, end of dosing [EOD]), at which time a unilateral venography assessment of the operated leg will be performed within 24 hours of the last dose of apixaban or matching apixaban placebo. Further details regarding the venography are provided in Section 9.2.1, Assessments for DVT.

Unscheduled Visits

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 PD samples (except D-dimer) should be collected as soon as practically possible for any subject that experiences symptomatic thrombotic or bleeding events.

Early Withdrawal

Subjects who do not receive the full infusion of JNJ-64179375 or prematurely discontinue dosing with apixaban or matching apixaban placebo before the end of the double-blind dosing phase will be instructed to return to the study site at the originally scheduled Day 10-14 visit (not earlier) to conduct assessments, including the venography assessment of the operated leg. If a subject has a suspected symptomatic DVT prior to the Day 10-14 visit, an ultrasound will be performed. If the ultrasound confirms symptomatic proximal DVT, a subsequent venography assessment is not required. In addition, if the subject is diagnosed with a PE as defined in

Section 9.2.2, Assessments for PE, a venography assessment is not required. Refer to Section 9.2, Efficacy Evaluations for further details regarding anticoagulation treatment. If the ultrasound is negative or confirms a distal DVT, the venography assessment should be conducted on the Day 10-14 visit. Subjects should complete the remaining visits through the Week 18 assessments as indicated in the Time and Events Schedule.

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 mail 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. Refer to Section 10.2, Discontinuation of Study Drug/Withdrawal from the Study for additional details.

9.1.4. Follow-Up Phase

The first follow-up visit will occur approximately 3 weeks following the Day 10-14 visit, with subsequent follow-up visits occurring until Week 18 as described in the Time and Events Schedule. Reasonable attempts, as defined in Section 10.2, Discontinuation of Study Drug/Withdrawal from the Study should be made to conduct the follow-up visit(s) at the scheduled time points. Subjects will continue to be monitored for safety, including bleeding events and efficacy events, according to the time points indicated in the Time and Events Schedule.

9.2. Efficacy Evaluations

Efficacy evaluations, including the unilateral venography assessment of the operated leg and assessments of symptomatic DVT, PE, death, or other thrombotic events (ie, MI, ischemic stroke, and peripheral arterial embolism) will be performed according to the time points in the Time and Events Schedule to assess the primary, secondary, and exploratory efficacy outcomes. All venography assessments, ultrasound evaluations for suspected symptomatic DVT, as applicable, and evaluations for suspected PE or other thrombotic events will be performed and read locally and sent for central adjudication by the independent CEC. The central adjudication evaluations will not be provided to the local sites. The CEC-adjudicated and investigator-reported results on efficacy and safety outcomes will be provided for the unblinded data reviews and the interim analyses. The CEC-adjudicated events will be used in the final analysis. Refer to Section 11.11.4, Clinical Events Committee for additional details on the composition of the CEC and their responsibilities.

If an event or condition requiring anticoagulant treatment occurs during the double-blind dosing phase then the blinded apixaban or matching apixaban placebo should be discontinued. Antithrombotic therapy management for conditions requiring anticoagulation (eg, new onset

atrial fibrillation, symptomatic DVT, or symptomatic PE) will be at the discretion of the local investigator. It is recommended that the event be treated with either a DOAC only or LMWH with a transition to a DOAC. If knowledge of the likely treatment group would change the planned event management strategy then local laboratory coagulation testing may also be considered, with a normal TT likely indicating the absence of JNJ-64179375. For asymptomatic distal DVT detected by venography, a possible management approach would be to use serial ultrasound to assess for any proximal progression and withhold anticoagulant therapy unless proximal progression is observed. If it is decided that treatment is to be given, the same approach as suggested for proximal DVT or PE is recommended.

In this study, all suspected symptomatic efficacy (thrombotic) events will also be captured as adverse events of special interest, which are defined in Section 9.7.2, Adverse Events of Special Interest.

9.2.1. Assessments for DVT

Unilateral Venography

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 consistent with the technique described by Rabinov and Paulin.[26] Evaluable venography assessments require the visualization of all of the deep veins except for the muscular, anterior tibial, and deep femoral veins. A diagnosis of DVT will be made if a constant intraluminal filling defect is observed in at least 2 images. 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. Details regarding the timing of the venography assessment are provided in Section 9.1.3, Double-Blind Dosing Phase.

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.

9.2.2. Assessments for PE

For all subjects with symptoms of PE, spiral computed tomography (CT), pulmonary angiography, or perfusion/ventilation lung scintigraphy 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 CT scan of the chest
- Positive direct 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 diagnosed with a PE meeting the above definitions, a subsequent venography assessment of the operated leg is not required.

9.2.3. Assessments for Other Thrombotic Events

Other thrombotic events will include MI, ischemic stroke, and peripheral arterial embolism. In addition, events that appear suggestive of study endpoints (eg, transient ischemic attack [TIA], unstable angina) will be reported by the investigator and reviewed by the CEC to ascertain if a thrombotic event has occurred. The investigator will use his/her medical judgment based upon the definitions below to determine if a thrombotic event has occurred.

Myocardial Infarction

The diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or postmortem pathologic findings); and
- Supporting information derived from the clinical presentation, ECG changes, or myocardial or coronary artery imaging.

Stroke

Stroke is defined as a new, sudden, focal neurologic deficit resulting from a presumed cerebrovascular cause and not due to a readily identifiable cause such as trauma, a tumor, or seizure.

If an event matching this definition lasts less than 24 hours it will be considered a TIA unless imaging confirmation of infarction is obtained. Investigators will further classify the strokes based upon imaging studies.

- Primary ischemic infarction – stroke without focal collections of intracranial blood confirmed by imaging. The occurrence of hemorrhagic conversion of a primary ischemic infarction will be recorded.
- Primary hemorrhagic – stroke with focal collections of intraparenchymal blood. The diagnosis of primary hemorrhagic stroke can only be made with imaging studies. It may include intraventricular hemorrhage.
- Subarachnoid hemorrhage – the diagnosis requires documentation by an imaging study
- Uncertain – no imaging or autopsy available

Other events of intracranial bleeding such as subdural hematoma and epidural hematoma will not be considered to be a stroke as they are usually traumatic in nature.

Peripheral Arterial Embolism

A peripheral arterial embolism is defined as an abrupt vascular insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (eg, trauma, atherosclerosis, instrumentation). In the presence of atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities should be made with caution and requires angiographic demonstration of abrupt arterial occlusion.

9.3. Pharmacokinetics and Immunogenicity

Plasma samples will be used to evaluate the PK of JNJ-64179375, as well as the development of ADAs to JNJ-64179375 (immunogenicity).

9.3.1. Evaluations

Samples for analysis of JNJ-64179375 plasma concentration will be collected for all subjects over time as specified in the Time and Events Schedule but will only be analyzed for subjects randomly assigned to JNJ-64179375. Dense PK sampling will be conducted at all sites for subjects at all visits in Part 1 until approximately up to the first 200 subjects have been randomized. Thereafter, the remaining subjects in Part 1 and all subjects in Part 2 will have PK blood samples collected at a limited number of visits (ie, sparse PK sample collection). The exact date and time of each PK blood sample collection will be recorded even if the time deviates slightly from the scheduled time of collection. Subjects who experience a bleeding event or symptomatic thrombotic event should have PK samples collected as soon as practically possible after the event occurs.

The timing of PK samples may be changed to ensure thorough PK monitoring; however, the total number of samples and/or the volume of blood drawn will not exceed the amount stated in Section 9.1.1, Overview without prior IEC/IRB and health authority approvals. Of note, additional blood samples may be collected for immediate safety monitoring of a subject and do not require prior IEC/IRB and health authority approvals.

Samples collected for analyses of JNJ-64179375 plasma concentration and antibodies to JNJ-64179375 may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, or for further characterization of immunogenicity. Genetic analyses will not be performed on these plasma samples. Subject confidentiality will be maintained. Additional information about the collection, handling, and shipment of biological samples will be provided in the laboratory manual.

9.3.2. Analytical Procedures

Pharmacokinetics

Blood samples will be collected from all subjects according to the Time and Events Schedule and analyzed to determine plasma concentrations of JNJ-64179375 in appropriate samples using

a validated, specific, and sensitive immunoassay method by or under the supervision of the sponsor.

Immunogenicity

The detection and characterization of antibodies to JNJ-64179375 will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to JNJ-64179375 will also be evaluated for JNJ-64179375 plasma concentration to enable interpretation of the antibody data. The Day 1, 0 hours (predose) ADA sample may be used for baseline characterization for both the PK and immunogenicity assays.

9.3.3. Pharmacokinetic Parameters

The PK parameters to be calculated following the single IV dose of JNJ-64179375 will include, but are not limited to, the following:

C_{max}	maximum concentration during a dosing interval
AUC_{inf}	area under the plasma concentration versus time curve from time 0 to infinity
$t_{1/2}$	terminal half-life
CL	total clearance of drug after IV administration
V_Z	apparent volume of distribution in the terminal phase

Additional PK parameters may be determined, as appropriate.

Based on the individual plasma concentration-time data using the actual dose taken and the actual sampling times, PK parameters and exposure information of JNJ-64179375 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. A separate population PK modeling plan will be developed before the first subject is consented and the population PK modeling results will be reported separately, in a document other than the clinical study report (CSR).

9.3.4. Immunogenicity Assessments

Blood samples for antibodies to JNJ-64179375 will be collected from all subjects according to the Time and Events Schedule but will only be analyzed in plasma samples for subjects randomized to JNJ-64179375. The exact date and time of each blood sample collection will be recorded. Additionally, samples should also be collected at the final visit from subjects who are discontinued from treatment or withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Plasma samples will be screened for antibodies binding to JNJ-64179375 and the titer of confirmed positive samples will be reported. Other analyses (eg, neutralization capacity) may be performed to further characterize the immunogenicity of JNJ-64179375.

9.4. Pharmacodynamic/Biomarker Evaluations

All subjects will have plasma samples collected to assess PD markers as specified in the Time and Events Schedule. The assay plan is designed to assess target engagement and the mechanism of action with a battery of PD assessments. Pharmacodynamic evaluations will include the coagulation assays (ie, TT, ECT, PT, aPTT) and a D-dimer assessment. Subjects who experience a bleeding event or symptomatic thrombotic event should have PD samples (except D-dimer) collected as soon as practically possible after the event occurs. Samples on Day 1 will be obtained before the study drug is administered and at 1 hour after the start of the IV infusion and all assays will be performed by a central specialty laboratory. Additional information about the collection, processing, storage, and shipment of PD samples will be provided in a separate laboratory manual. It is expected that apixaban would have no effect or minimal effects on all of the coagulation assays and therefore, analysis of the apixaban samples is not planned.

To maintain the blind of the study, the investigator should not measure coagulation assays locally unless considered necessary for subject 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.

Thrombin Time

The thrombin clotting time (designated TT) is a simple test that measures the time for clot formation in citrated plasma after the addition of thrombin. It reflects the effect of thrombin to cleave fibrinogen to form fibrin. Heparin and direct thrombin inhibitors such as hirudin, argatroban, and dabigatran are inhibitory, LMWH is partially inhibitory, and apixaban is inactive.

Ecarin Clotting Time

The ECT test is based on the cleavage of prothrombin by ecarin, a highly purified metalloprotease isolated from the venom of the saw-scaled viper Echis carinatus. Ecarin generates meizothrombin from prothrombin, which is proteolytically active and can cleave fibrinogen to form a fibrin clot. Meizothrombin, like thrombin, is inactivated by hirudin and other direct thrombin inhibitors, but is unaffected by heparin (as the heparin-antithrombin complex cannot inhibit meizothrombin due to steric hindrance). JNJ-64179375 is able to block the binding of meizothrombin to fibrinogen and therefore inhibit clot formation. This assay may offer potential advantages in sensitivity and useful range over the TT test.

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 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, international normalized ratio, have been 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.

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 and direct thrombin inhibitors, including hirudin, argatroban, and dabigatran have an effect on the assay.

D-dimer

The various states of coagulation activation that occur in vivo lead to the production of thrombin and then, fibrin. What follows is a reactive fibrinolysis, during which plasmin breaks down fibrin. The D-dimer is the ultimate degradation product of fibrin. The presence of D-dimer in plasma is an indirect marker of a coagulation activation followed by a reactive thrombolysis. Increased levels 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.

9.5. Pharmacokinetic/Pharmacodynamic Evaluations

The PD variables that will be evaluated for possible PK/PD relationships are TT, PT, and aPTT (refer to Section 9.4, Pharmacodynamic/Biomarker Evaluations for a description of the PD variables). The PK of JNJ-64179375 to be used as predictor variables are C_{max} and AUC_{inf} (but not limited to) obtained by population PK analysis as described in Section 9.3.3, Pharmacokinetic Parameters. The relationship between TT, PT, and aPTT and plasma exposure metrics (C_{max} and AUC_{inf}) will be evaluated using models that will further be detailed in a separate population PK modeling plan.

9.6. Health Resource Utilization

Health resource utilization data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. Key parameters of healthcare

resource utilization will be collected for all subjects and compared between the treatment groups. The data collected will include the following:

- Total length of initial hospitalization and length of stay for each specialized unit by level of care (eg, ward type, intensive care unit and cardiac care unit stays)
- Rehospitalization for any reason through 18 weeks of follow up
- Any scheduled and unscheduled visits to healthcare providers for study outcomes, any other medical reasons, and diagnostic procedures used in relation to study outcomes through 18 weeks of follow up
- Discharge destination from the initial or subsequent hospitalization(s) (eg, home, rehabilitation)
- Details related to the management of any bleeding complications, (eg, procedures, extension of hospital stay, blood and/or plasma products)
- Details regarding the management of subjects who develop symptomatic VTE

9.7. Safety Evaluations

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule: adverse events, including serious adverse events, adverse events of special interest (ie, bleeding events, infusion reactions, hypersensitivity reactions, and wound or joint complications), clinical laboratory tests (ie, hematology, clinical chemistry, urinalysis), vital signs measurements (blood pressure, pulse/HR, temperature), and physical examinations. Safety evaluations may also be performed at unscheduled time points, if deemed by the investigator or appropriate designee as necessary to ensure the safety of the subject.

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 endpoint is reached.

9.7.1. Adverse Events

Adverse events, including serious 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. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

All adverse events, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until the completion of the subject’s last study-related procedure. Refer to Section 12.3.1, All Adverse Events for additional details.

Any wound or joint complications occurring after the TKR surgery will be specifically evaluated as described in Section 9.7.2.3, Wound or Joint Complications. In addition, knee joint range of motion will be evaluated at Week 18 as described in Section 9.7.6, Physical Examination.

9.7.2. Adverse Events of Special Interest

In this study, adverse events of special interest are:

- Bleeding events (Section 9.7.2.1, Bleeding Events)
- Infusion or hypersensitivity reactions (Section 9.7.2.2, Infusion or Hypersensitivity Reactions)
- Wound or joint complications (Section 9.7.2.3, Wound or Joint Complications)

As previously noted in Section 9.2, Efficacy Evaluations, all suspected symptomatic efficacy (thrombotic) events will also be captured as adverse events of special interest.

9.7.2.1. Bleeding Events

9.7.2.1.1. 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 Time and Events Schedule.

The investigator's classification of bleeding events according to the protocol classification will be collected in the eCRF (refer to Attachment 2). In addition, Guidelines for Reporting Bleeding Event Verbatim Terms will be provided as noted in Section 15, Study-Specific Materials. Additional information, including but not limited to the list below, will be collected for subjects with bleeding events and entered into the eCRF:

- Location of the bleeding
- 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
- Any associated blood transfusions and products
- 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 (refer to Section 11.11.4, Clinical Events Committee for additional details).

9.7.2.1.2. Approach to Subjects With a Bleeding Event

There is no antidote for either study drug. If a subject has a bleeding event requiring intervention during the study, the following measures should be considered for both study drugs:

- Discontinue the study drug (refer to Section 10.2, Discontinuation of Study Drug/ Withdrawal from the Study)
- 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

If bleeding cannot be controlled by these measures, consider administration of 1 of the following procoagulants according to the dosages and dosing schedules that are recommended in their respective package inserts (Note: consultation with a coagulation expert is recommended before use):

- PCC
- Activated PCC
- Factor VIIa

Of note, protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of either study drug. In a rat-tail transection bleeding model, Beriplex (4-factor PCC) and FEIBA (activated 4-factor PCC) returned bleeding times to control levels while TXA and activated Factor VIIa (NovoSeven) did not shorten the bleeding times after dosing with JNJ-64179375 at the doses studied. See Section 1.1.2.3, Parts 2 and 3 for reversal of PD effects for JNJ-64179375. Reversal of the PD effects of apixaban, as demonstrated by changes in the thrombin generation assay, was evident at the end of the infusion and reached baseline values within 4 hours after the start of a 30-minute infusion of 4-factor PCC in healthy subjects. However, there is little clinical experience with the use of 4-factor PCC products to reverse bleeding in individuals who have received apixaban. Currently, there is no experience with the use of recombinant Factor VIIa in individuals receiving apixaban.

Due to its high molecular weight, JNJ-64179375 is not expected to be dialyzable. Hemodialysis decreased the AUC of apixaban by 14% in subjects with end-stage renal disease when a single dose of apixaban 5 mg was administered orally. Therefore, hemodialysis is unlikely to be an effective means of managing an overdose with apixaban or to manage bleeding with JNJ-64179375.[8]

In those cases where approaches to reduce the blood levels of the study drug are being considered:

- In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean AUC of apixaban by 50% and 27%, respectively, and had no impact on C_{max}. The mean half-life of apixaban decreased from 13.4 hours when apixaban was administered alone to 5.3 hours and 4.9 hours, respectively, when activated charcoal was administered 2 and 6 hours after apixaban. Therefore, administration of activated charcoal may be useful in the management of an overdose with apixaban or accidental ingestion.[8]
- JNJ-64179375 has a plasma half-life of approximately 25 days as estimated from preliminary PK data in healthy subjects. Administration of IV immunoglobulins would be expected to increase the clearance of JNJ-64179375 by saturation of neonatal Fc receptors. A therapeutic plasma exchange to remove JNJ-64179375 could also be considered (estimated removal would be about 60% to 70% with 1 plasma volume exchange).[33]

9.7.2.2. Infusion or Hypersensitivity Reactions

Infusion reactions or hypersensitivity reactions (eg, anaphylaxis, urticaria, dyspnea, hypotension) have been observed with the administration of monoclonal antibodies and may occur at any time during the administration of the IV study drug or within the first few hours after administration. Serum sickness-like reactions (also known as delayed hypersensitivity reactions) have been observed between 1 to 14 days after treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgia, polyarthralgia, hand and facial edema, and/or dysphagia.

The IV study drug must not be administered to individuals with known or suspected intolerance or hypersensitivity to any biologic medication or known allergies or clinically significant reactions to murine, chimeric, or human proteins, monoclonal antibodies or antibody fragments, or to any of the excipients of the JNJ-64179375 formulation used in this study (refer to Section 4.2, Exclusion Criteria).

A physician must be immediately available at the site at all times during the administration of the study drug infusion as noted in Section 6, Dosage and Administration. All subjects will be carefully observed for symptoms of an infusion reaction during the infusion and for at least 90 minutes after the start of the IV infusion and for the development of any allergic reaction during the study. The investigator should use clinical judgment in assessing the intensity of any infusion reactions. If an infusion reaction is observed, treatment such as oral paracetamol/acetaminophen and/or oral antihistamines may be administered. Details regarding the infusion reaction, including any medications administered, should be captured in the eCRF.

The following precautions should be applied during a study infusion:

- Before an infusion is started, the appropriate personnel, medications (eg, epinephrine, inhaled β-agonists, antihistamines, and corticosteroids), and other requirements to treat allergic reactions, including anaphylaxis, must be readily available.

- If a subject has a moderate or severe infusion reaction, the infusion should be terminated immediately and the subject should be treated appropriately according to institutional guidelines.
- Subjects discontinuing the study drug due to an infusion reaction will be asked to return for required assessments at all scheduled visits through the Week 18 visit. Refer to Section 10.2, Discontinuation of Study Drug/Withdrawal from the Study for additional details regarding subject discontinuation.

9.7.2.3. 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 Time and Events Schedule. 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.

9.7.3. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be collected. 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 postoperative 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 and as part of standard postoperative care following surgery. Hematology and chemistry laboratory tests and a urine sample for urinalysis will be obtained before dosing (0 hour) and performed by the central laboratory. The following tests will be performed by the central laboratory:

- Hematology Panel

-hemoglobin	-platelet count
-hematocrit	-mean corpuscular hemoglobin (MCH)
-red blood cell (RBC) count	-mean corpuscular hemoglobin concentration (MCHC)
-WBC count with differential	Mean corpuscular volume (MCV)

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.

- Serum Chemistry Panel

-sodium	-alkaline phosphatase
-potassium	-creatine kinase (CK) with myocardial band fractionation, if elevated
-chloride	-lactic acid dehydrogenase (LDH)
-bicarbonate	-uric acid
-blood urea nitrogen (BUN)	-calcium
-creatinine	- phosphate
-glucose	-albumin
-aspartate aminotransferase (AST)	-total protein
-alanine aminotransferase (ALT)	-cholesterol
-gamma-glutamyltransferase (GGT)	-triglycerides
-total, direct and indirect bilirubin	-magnesium
-globulin	

- Urinalysis

Dipstick	Sediment (if dipstick result is abnormal)
-specific gravity	-RBCs
-pH	-WBCs
-glucose	-epithelial cells
-protein	-crystals
-blood	-casts
-ketones	-bacteria
-bilirubin	
-urobilinogen	
-nitrite	
-leukocyte esterase	

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.

9.7.4. Electrocardiogram

A 12-lead ECG will be performed during screening. During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital signs measurements are scheduled for the same time point as ECG recording, it is recommended that the procedures be performed in the following order: ECG, vital signs, and blood draw.

9.7.5. Vital Signs (temperature, heart rate, blood pressure)

Vital signs measurements will be obtained at the time points indicated in the Time and Events Schedule.

Blood pressure and pulse/HR measurements will be assessed with subjects in the supine position with a completely automated device. Manual techniques will be used only if an automated device is not available. Single measurements at each time point will be made. However, if any clinically significant abnormal values are detected (systolic blood pressure >160 or <90 mmHg, diastolic blood pressure >100 mmHg, HR <40 or >100 beats per minute) then repeat measurements will be performed at the discretion of the investigator.

Blood pressure and HR measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

The subject's temperature should also be obtained.

9.7.6. 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 9.7.2.1.1, 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 Day -1 or prior to dosing on Day 1 and the final visit. Scales used should be calibrated according to the standard operating procedures at the study site to assure weight is accurate.

The physical examination will be conducted at the time points indicated in the Time and Events Schedule. An assessment of the wound will be made at all visits as part of the adverse event assessment and the final physical examination will assess the range of motion of the operated joint. 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.

9.8. Sample Collection and Handling

The actual dates and times of sample collection must be recorded on the laboratory requisition form. 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 (USP) (or equivalent) and charged with a volume equal to the dead space volume of the lock. Blood samples for PK and PD assessments on Day 1 post dosing should be collected in the opposite arm as the infusion of JNJ-64179375 or placebo.

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

Instructions for the collection, handling, storage, and shipment of all blood and urine samples are found in the separate laboratory manual 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.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY DRUG/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she has completed the Week 18 visit of the follow-up phase.

Subjects who prematurely discontinue the study drug for any reason before completion of the double-blind dosing phase will be considered to have completed the study if they have completed the Week 18 visit. A subject who dies will be considered to have completed the study.

10.2. Discontinuation of Study Drug/Withdrawal from the Study

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, the study site should collect as much follow-up visit information as possible, by contacting the subject by telephone or by mail. 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 study drug or withdraws may not be assigned to another subject. Subjects who withdraw will not be replaced.

Discontinuation of Study Drug

A subject will not be automatically withdrawn from the study if he or she has to discontinue the study drug before the end of the double-blind dosing phase.

Subjects who discontinue the study drug before the end of the double-blind dosing phase will be instructed to return to the study site, if possible, to conduct assessments, including venography assessments of the operated leg as described in Section 9.1.3, Double-Blind Dosing Phase. If a subject withdraws from the study before the end of the double-blind dosing phase, EOD and follow-up assessments should be obtained.

A subject's study drug must be discontinued for any of the following reasons:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study drug
- The subject requests to discontinue the study drug permanently

- Development of any condition that requires open-label treatment with an anticoagulant or other prohibited medication
- Bleeding into a critical site, (eg, intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal)
- Active uncontrolled hemorrhage
- At the (exceptional) request of the sponsor

Withdrawal From the Study

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. The recording of withdrawal of consent in the eCRF for this study will occur 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 poststudy drug follow-up information should he or she decide 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, he or she should be contacted and the study site should collect as much follow-up information as possible. This includes contacting the subject or the subject's alternative means of contact (eg, subject's children, spouse, significant other, caretaker, legal representative or health care professional), by telephone or mail to determine vital status and if an endpoint event has occurred, as agreed to by the subject during the initial informed consent process. If applicable, vital status may be obtained by reviewing the subject's medical or public records, unless this process is not allowed by 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.

When a subject withdraws consent before completing the study, it is not required for he/she to give a reason. If the reason for the withdrawal is known, it should be documented in the eCRF and in the source document.

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 law permits. The

measures taken to follow up must be documented. A subject will be considered lost to follow up only after all means of all subsequent contact have been exhausted.

11. STATISTICAL METHODS

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 a statistical analysis plan (SAP), which will be prepared for Part 1 before the first subject is consented for Part 1. For Part 2, a draft SAP will be prepared before the first subject is consented into Part 1 and an updated Part 2 SAP based on the Part 1 data will be prepared before the first subject is consented in Part 2.

In Part 1, the intent is to escalate across the planned doses (0.3 to 0.6 to 1.2 mg/kg) of JNJ-64179375 based on the OC review of the totality of the data but with a focus on bleeding events. Specific analyses to be reviewed (eg, continual reassessment or escalation with overdose control methods) and dose-escalation decision guidelines will be included in the OC charter. After all subjects are expected to have completed the Day 10-14 visit for Part 1, an unblinded data review is planned and the selection of the dose range and doses for Part 2 will be based on the evaluation of the totality of the data but with a focus on the any bleeding and total VTE endpoints. Analyses to aid in dose selection will be prespecified in the OC charter and the Part 1 SAP. No formal hypothesis testing is planned for Part 1 due to the limited sample size. Historical apixaban bleeding and VTE event rates may also be considered in making decisions.

In Part 2, this study will use an adaptive design intended to optimize data collection for dose-response modeling. In Part 2, the primary goal is to assess the efficacy (total VTE endpoint) dose-response relationship of JNJ-64179375. A hybrid methodology that combines aspects of multiple testing with modeling techniques (MCP-Mod) will be used for evaluating dose-response trends and estimating the dose-response relationships for the efficacy and bleeding endpoints for JNJ-64179375.[2,3,25] The sample size for Part 2 may be adjusted based on the observed bleeding and total VTE event rates in Part 1. Additional details are provided in Section 11.3, Efficacy and Bleeding Analyses.

If a sufficient number of JNJ-64179375 doses (ie, 4 or more) are studied in Part 2 then dose-response modeling using the MCP-Mod approach will be the primary analysis strategy. If the number of JNJ-64179375 doses is not sufficient to support the MCP-Mod approach then linear dose-response modeling (if 3 doses are studied), or pairwise comparisons (if 2 doses are studied), will be the primary analysis strategy.

An unblinded data review is planned for Part 1 after all subjects are expected to have completed the Day 10-14 visit to determine the dose range and doses of JNJ-64179375 for Part 2. Two planned, unblinded interim analyses and 1 unblinded administrative interim analysis are intended for Part 2 of this study. Refer to Section 11.10, Interim Analyses for further details.

11.1. Analysis Datasets

The 2 elements that define an analysis data set are:

- The analysis population, which specifies those subjects who will be included in an analysis
- The observation period, which specifies the time window within which data will be included in an analysis

Efficacy Analyses

Two populations will be used in the efficacy analyses:

- Modified Intent to Treat (ITT): all randomized subjects with an evaluable venography assessment or a confirmed symptomatic VTE event, or any death.
- Efficacy Per Protocol: all randomized subjects with no major protocol deviations (to be defined in the SAP) and an evaluable venography assessment within 24 hours after the last dose of the oral study drug or with confirmed symptomatic VTE within 2 days of the last dose of oral study drug, or any death within 2 days of the last dose of oral study drug. Subjects without symptomatic VTE or death must also have received the single complete infusion of JNJ-64179375 or at least 18 doses of oral apixaban.

The 2 observation periods to be used in the efficacy analyses include the following:

- Up to Day 10-14 visit (venography assessment)
- Up to the Week 18 visit

The primary efficacy endpoint analysis (total VTE) will use the modified ITT population up to the Day 14 observation period. Additional details will be provided in the SAP.

Bleeding Event Analyses

Two populations will be used in the bleeding event analyses:

- Safety: all randomized subjects who received at least 1 dose (partial or complete) of active study drug
- Safety Per Protocol: all randomized subjects with no major protocol deviations who received the single complete infusion of JNJ-64179375 or at least 18 doses of oral apixaban or with a bleeding event centrally adjudicated by the CEC within 2 days of the last dose of oral study drug

The 3 observation periods to be used in the bleeding event analyses include the following:

- Up to Day 10-14 visit (venography assessment)
- Up to the Week 5 visit
- Up to the Week 18 visit

The primary bleeding event analysis (any bleeding) will use the safety population up to the Day 10-14 visit observation period.

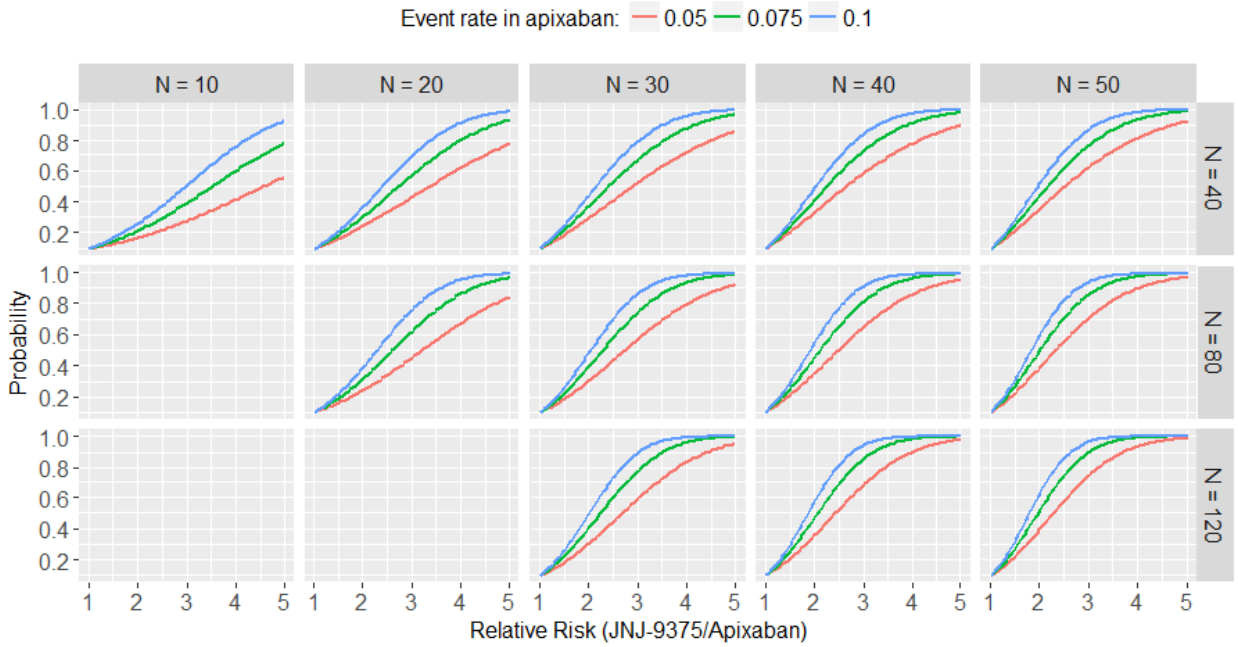
11.2. Sample Size Determination

A total of 1,500 subjects are planned for this study, of which up to 300 subjects will be enrolled in Part 1 and the remainder for the entire study will be enrolled in Part 2. In Part 1, the sample

size is not based on hypothesis testing but rather on making a preliminary assessment of the bleeding risk for the doses of JNJ-64179375. The event rate of any bleeding up to 14 days for apixaban 2.5 mg twice daily is expected to be between 5% and 10%. Figure 2 shows the probability to flag a higher event rate compared to apixaban for any dose of JNJ-64179375 in Part 1, assuming that the true underlying bleeding event rate in the apixaban group is 5%, 7.5%, or 10%. The figure presents the numbers of subjects in the JNJ-64179375 and apixaban treatment groups in rows and columns, respectively. The assumed event rate in the JNJ-64179375 group is presented as the relative risk to apixaban in the horizontal axis; the statistical comparison is based on the difference between event rates.

When the true underlying event rate in the apixaban group is 7.5%, there is a 67% probability for a dose of JNJ-64179375 to have the lower bound of the 1-sided 90% CI for between-treatment difference exclude 0 if the true relative risk (or risk ratio) is 3 (ie, the true underlying event rate in the JNJ-64179375 group is 22.5%), with 40 subjects in the JNJ-64179375 group (ie, any 1 planned cohort of JNJ-64179375 subjects) and 30 subjects in the apixaban group (ie, pooled apixaban subjects from 3 planned cohorts). The probability will increase to 81% when the dose of JNJ-64179375 is repeated in another planned or optional cohort, where there will be 80 subjects in the JNJ-64179375 treatment group and 40 subjects in the pooled apixaban group.

Figure 2: Probability to Flag a Higher Event Rate in the JNJ-64179375 Group Than in the Apixaban Group at a 1-Sided, 10% α-Level



JNJ-9375=JNJ-64179375

In Part 2, it is anticipated that 10% to 20% of subjects will either not have the venography assessment of the operated leg performed as scheduled or will not have an evaluable venography assessment for any DVT or proximal DVT. Assuming that 80% of venography assessments are

evaluable and the true underlying total VTE event rates are 15%, 10%, 8%, and 6% at potential doses of JNJ-64179375 of 0.3, 0.6, 0.9, and 1.2 mg/kg, respectively, with a total sample size of 1,200 subjects, the study is expected to have over 90% power to declare proof-of-efficacy, which is defined as either a statistically significant dose-response trend or a total VTE event rate lower than 30% in the pooled doses of JNJ-64179375 at a 1-sided, 2.5% α-level. The exact power will vary because of the nature of the adaptive study design.

For comparison with apixaban in Part 2, if the true underlying total VTE and any bleeding event rates are as specified in Table 7, a simulation study demonstrates that there will be approximately 90% probability to identify a dose within the dose range of 0.3 to 1.2 mg/kg, of which both the model-predicted total VTE and any bleeding event rates met the prespecified noninferiority (NI) criterion (the upper bound of the 1-sided 90% CI for the odds ratio [JNJ-64179375 to apixaban] is equal to or lower than 1.5 for total VTE and any bleeding events).

Table 7: Assumed Efficacy and Safety Event Rates by Treatment Group in Sample Size Determination for Part 2

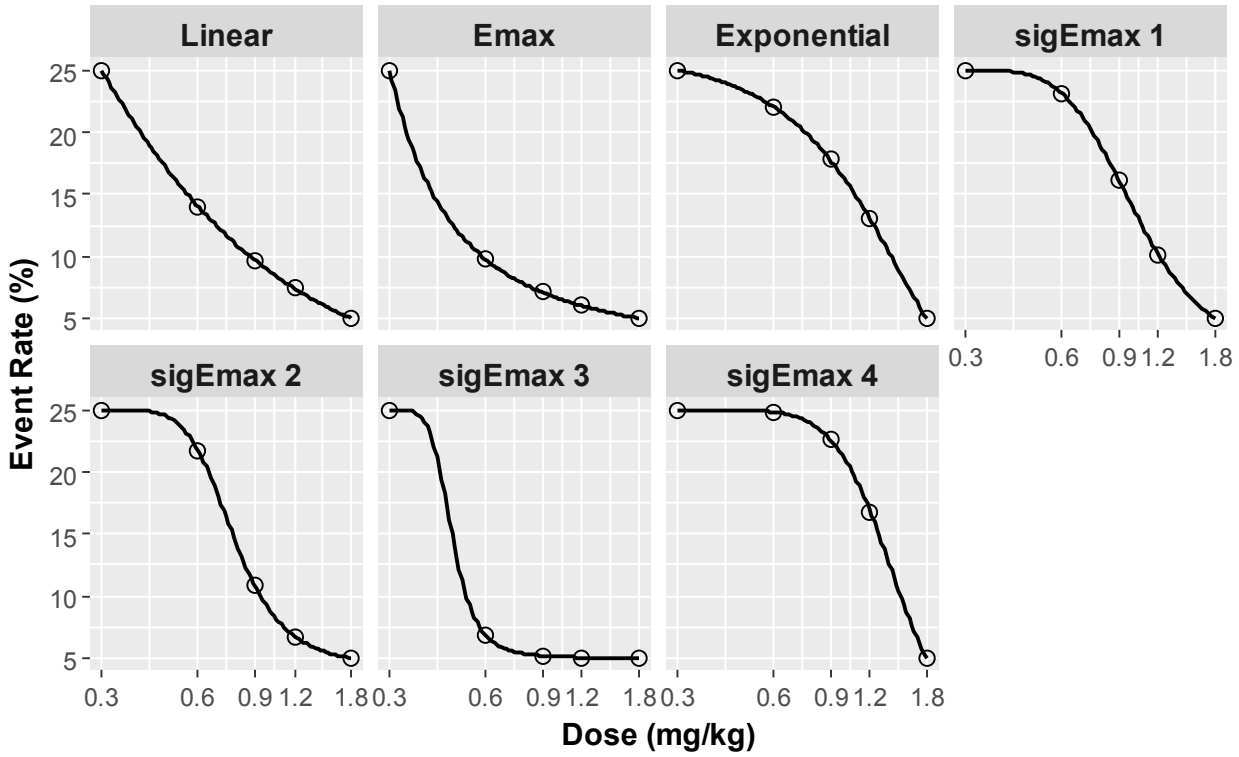
	JNJ-64179375				Apixaban
	0.3 mg/kg	**0.6 mg/kg**	**0.9 mg/kg**	**1.2 mg/kg**	**2.5 mg bid**
Total VTE (Efficacy)	15%	10%	8%	6%	15%
Any Bleeding (Safety)	5%	6%	7%	8%	8%

bid=twice daily; VTE=venous thromboembolism

11.3. Efficacy and Bleeding Analyses

A dose-response trend will be assessed with respect to the primary efficacy (total VTE) and safety (any bleeding) endpoints in Part 2. Depending on the number of doses studied, a set of up to 7 candidate models (doses are in logarithm scale) will be used to cover a suitable range of possible efficacy dose-response shapes (linear, Emax, exponential, sigEmax1, sigEmax2, sigEmax3, and sigEmax4) (see Figure 3).

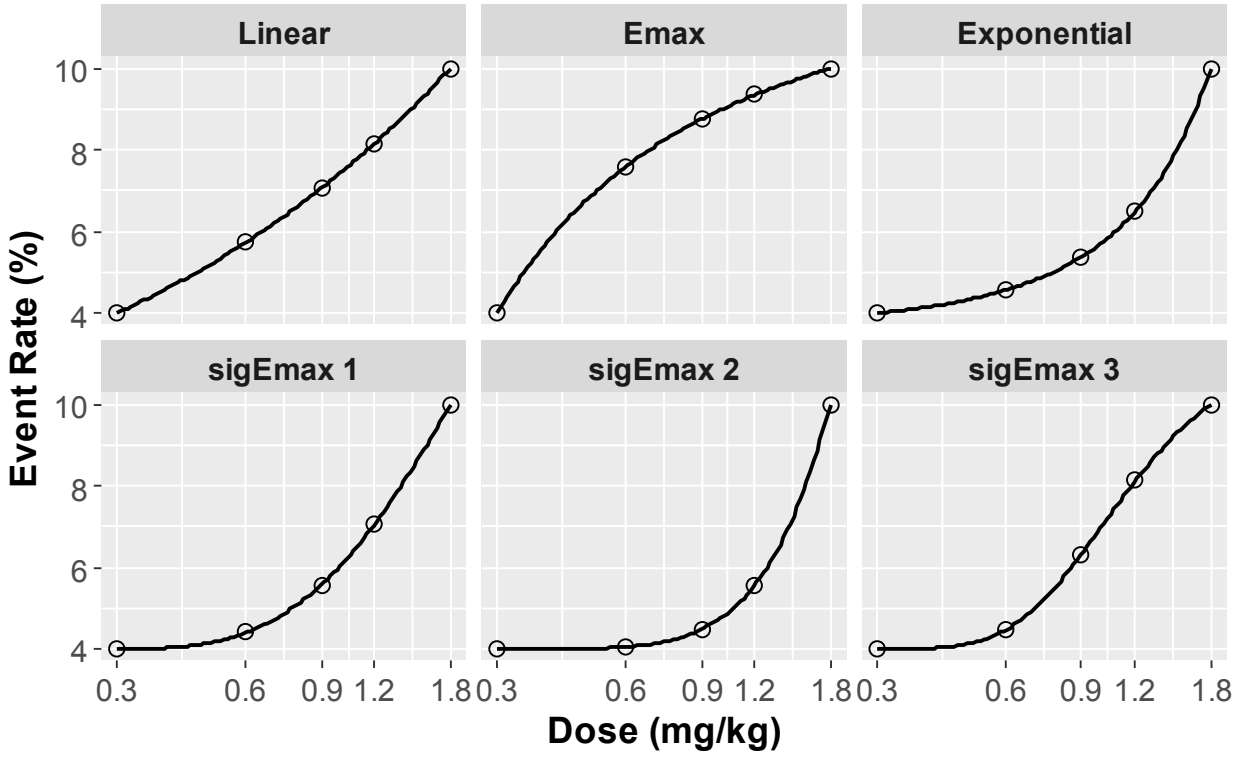
Figure 3: Candidate Models for Total VTE (Efficacy)



VTE=venous thromboembolism

Similarly, a set of up to 6 candidate models will be used to cover a suitable range of safety dose-response shapes (linear, Emax, exponential, sigEmax1, sigEmax2, and sigEmax3) (see Figure 4). The set of safety candidate models used will be similarly chosen as for the efficacy candidate models, which is dependent on the number of doses studied in Part 2.

Figure 4: Candidate Models for Any Bleeding (Safety)



Each of the dose-response shapes in the candidate set will be tested using the corresponding contrast *t*-test statistic, employing a critical value derived for the maximum of the *t*-test statistics (based on the associated multivariate *t*-distribution) to ensure appropriate multiplicity correction that preserves the Type I error rate. A dose-response trend is established for an endpoint when the maximum of the *t*-test statistics for the corresponding endpoint exceeds the critical value.

Predicted event rates at a specific dose will be derived for each candidate model. The weighted average of these predicted event rates (weights are determined by the model goodness-of-fit), will then be used to estimate the target dose.[4,16] The minimum dose that meets the NI efficacy criterion (defined as the upper bound of the 1-sided 90% CI for model-predicted JNJ-64179375/apixaban odds ratio less than 1.5) is considered as the minimum effective dose. The highest dose to be considered to proceed is the maximum dose that meets the NI safety criterion (defined as the upper bound of the 1-sided 90% CI for model-predicted JNJ-64179375/apixaban odds ratio less than 1.5). Any dose between the minimum effective dose and the highest dose to proceed is considered an eligible dose to be further studied in a subsequent study(ies). The final dose selection will be based on the consideration of the total benefit-risk balance.

The determination of the NI criterion above is based on 2 considerations: 1) distribution of the point estimate for the odds ratio for the given sample size when the NI criterion is met; and 2) the balance between the false-positive rate (incorrectly conclude an inferior dose to be comparable to apixaban) and the false-negative rate (incorrectly conclude an efficacious dose to be inferior to apixaban). With the given sample size and event rates as specified in Table 7, the

median corresponding odds ratio in 10,000 simulated studies is approximately 1.0 for total VTE and 0.94 for any bleeding. With the same assumptions, these NI criteria will yield approximately 90% probability to correctly identify an eligible dose for subsequent study(ies).

The details of the adaptive decision guidelines for adding and/or dropping treatment groups or changing the randomization ratio in Part 2 will be specified in the IDMC charter and the Part 2 SAP.

Prespecified clinical variables of interest for the efficacy subgroup analyses include region, age, sex, weight/body mass index, renal function, surgery duration, TXA use, tourniquet use, and mechanical VTE prophylaxis device use. The same variables will be used for safety subgroup analyses with the addition of aspirin/NSAID use.

11.4. Pharmacokinetic Analyses

Plasma concentrations of JNJ-64179375 will be listed for all subjects by time of collection and dose level. For each dose, descriptive statistics, including mean, median, standard deviation (SD), and coefficient of variation will be calculated for the plasma concentrations at each nominal sampling time. Plasma concentrations of JNJ-64179375 versus time profiles will be plotted for each subject based on actual sampling times, and mean concentration versus time profiles will be plotted for each dose level based on planned sampling times.

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 drug; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All plasma concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. 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 study report.

In addition, a population PK model will be developed and the dependence of PK of JNJ-64179375 on population covariates (eg, demographics, laboratory variables) will be evaluated. This will be performed using nonlinear mixed-effects modeling with the software package NONMEM©. The mean (and variance) values for specific PK parameters (eg, CL and V_z) will be estimated and the statistical significance of the relationships between the covariates and PK parameters will be evaluated. The results of this population PK (PK parameters signifying relationship between PK and various covariates) analysis will be reported separately, in a document other than the CSR.

11.5. Immunogenicity Analyses

The incidence of antibodies to JNJ-64179375 will be summarized for all subjects who receive a dose of JNJ-64179375 and have at least 1 appropriate sample obtained after study drug administration for the detection of antibodies to JNJ-64179375.

A listing of subjects who are positive for antibodies to JNJ-64179375 will be provided. The maximum titers of antibodies to JNJ-64179375 will be summarized for subjects who are positive for antibodies to JNJ-64179375.

Analyses of the impact of immunogenicity on PK, PD, PK/PD, efficacy, and safety endpoints will be performed to further characterize the immune responses that are generated.

11.6. Pharmacodynamic/Biomarker Analyses

The PD parameters are TT, ECT, PT, aPTT, and D-dimer. Descriptive statistics including mean, median, SD, minimum, and maximum will be provided for the PD parameters. The parameters of TT, PT, and aPTT may be statistically analyzed using mixed models. The mixed model for the change from baseline PD parameters will include dose and visit as fixed effects and subjects as random effects. The least-squares means for change from baseline and associated 95% CIs will be provided. Other PD parameters may be analyzed similarly.

11.7. Pharmacokinetic/Pharmacodynamic Analyses

The PK/PD relationships will be investigated graphically and, if appropriate, may be further analyzed using suitable statistical methods.

Plasma PK exposures (C_{max}, AUC_{inf}, and/or time-matched concentration) from the population PK model versus PD variables (eg, TT and aPTT) and safety/efficacy endpoints will be graphically examined. This can be accomplished by plotting relevant PD measures versus PK exposure parameters (quantiles/deciles) for preliminary assessment and possible model identification. If the graphical representation of the relationship indicates possible correlation, then these data may be analyzed statistically using a suitable model. For example, a mixed-effects linear model may be used to identify the possible relationship between PK and PD. Other models using time-matched concentrations with PD may also be used for exploring the relationship further, as appropriate. Other PD variables (eg, ECT) may be analyzed in a similar fashion. The details of the analyses plan will be presented in a population PK modeling plan that is separate from the SAP.

Preliminary assessments of these relationships will be made available to the IDMC at both interim analyses to support their evaluations.

11.8. Health Resource Utilization Analyses

Health resource utilization will be descriptively summarized by treatment group.

11.9. Safety Analyses

All safety data will be fully listed. The reporting of the safety data of all subjects receiving at least 1 active dose of JNJ-64179375 or apixaban will include the incidence and type of adverse events, plus absolute values and changes in blood pressure (systolic and diastolic), HR, clinical laboratory data, and physical examinations from predose to the final postdose time point.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify adverse events will be coded using the MedDRA. Treatment-emergent adverse events are adverse events with onset during the treatment 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, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Based on the mechanism of action of JNJ-64179375 and given that it is a monoclonal antibody, adverse events of special interest will include bleeding events, infusion reactions, hypersensitivity reactions, and wound or joint complications as described in Section 9.7.2, Adverse Events of Special Interest. Subjects with adverse events of special interest may be counted or listed using MedDRA SMQs (eg, hemorrhage excluding laboratory terms SMQ). All suspected symptomatic efficacy (thrombotic) events will also be captured as adverse events of special interest.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Part 1 and Part 2 SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the changes from baseline will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. 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.

Vital Signs

Descriptive statistics of temperature, HR, and blood pressure (systolic and diastolic) (supine) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

Physical Examination

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

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

11.10. Interim Analyses

Two planned, unblinded interim analyses will be conducted in Part 2 by the IDMC as part of the adaptive approach that will be used to guide decisions to drop and/or add doses of JNJ-64179375 and adjust the randomization ratio based on available efficacy, safety, PK, and PD 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
- Determine if a dose(s) 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)

These 2 interim analyses will be performed after approximately 400 and 800 subjects are enrolled and are expected to have completed the Day 10-14 visit. Depending on interim analysis results, possible modification options to study conduct are stopping the study prematurely for futility, adding/dropping a dose of JNJ-64179375, and adjusting randomization ratio based on optimization of the dose-response model estimation.

Subject randomization will be balanced until the first interim analysis. Adaptation guidelines, including futility, adding/dropping a dose, modification of the randomization ratio, will be specified in the IDMC charter and the Part 2 SAP.

Administrative Interim Analysis

An unblinded administrative interim analysis is planned to be conducted by the sponsor after all subjects are expected to have completed the Day 10-14 visit in Part 2 to facilitate additional study planning. Details of this interim analysis will be described in the Part 2 SAP. The conduct and integrity of the study will not be altered by the results of this interim analysis.

11.11. Committees

11.11.1. Operations Committee

During Part 1 of the study, an OC consisting of members of the academic leadership of the study, including the SC and IDMC chairpersons, and 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 1 to 3 weeks
- Determining the cohort sizes and number of cohorts for the up to approximately 300 unique subjects in Part 1
- Making dose-escalation decisions in Part 1, including but not limited to deciding whether to proceed with optional cohorts and at what dose(s)

- Reviewing the data for Part 1

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

After all the subjects to be enrolled in Part 1 are expected to have completed the Day 10-14 visit, an unblinded review of available preliminary safety, tolerability, efficacy, PK, and PD data will be conducted to determine the dose range and number of dose groups (maximum of 4 for JNJ-64179375 and 1 for apixaban) for Part 2. This Part 1 data review will be conducted by the OC, SC, IDMC, and the sponsor.

11.11.2. Independent Data Monitoring Committee

An unblinded IDMC will be established to monitor ongoing safety data in Part 2. The IDMC activities will include participation in the unblinded data review after all subjects in Part 1 are expected to have completed the Day 10-14 visit to determine the dose range and doses of JNJ-64179375 for Part 2 and to conduct the 2 planned interim analyses, applying the adaptive design rules for the study as described in Section 11.10, Interim Analyses. The IDMC will consist of individuals who are not participating in the conduct of the study and will include at least one medical expert in the relevant therapeutic area and at least one statistician. Following the interim analyses, the IDMC will be responsible for providing their recommendations for study modifications to the SC and sponsor. The IDMC responsibilities, authorities, and procedures will be documented in a separate charter.

11.11.3. Steering Committee

A SC with expertise in thrombosis, thromboprophylaxis, hematology, orthopedic surgery, and clinical studies will be commissioned to provide scientific leadership for both Parts 1 and 2 of the study. The SC 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. In Part 2, the SC will receive recommendations from the IDMC regarding suggested modifications to the study based on the review of the unblinded data by the IDMC. The sponsor, in collaboration with the SC, 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 SC will be documented in a separate charter.

11.11.4. Clinical Events Committee

A CEC will be established to review, adjudicate, and classify endpoint events in Parts 1 and 2 of the study 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 of the operated leg
- Suspected symptomatic DVT
- Suspected symptomatic PE
- Suspected bleeding events
- Suspected MI
- Suspected stroke
- Suspected peripheral arterial embolism
- 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. 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 both of the interim analyses. The CEC-adjudicated events will be used in the final analysis.

12. ADVERSE EVENT REPORTING

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 of special interest have been identified for this study and are described in Section 9.7.2, Adverse Events of Special Interest.

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. For some studies, subjects are not always able to provide valid verbal responses to open-ended questions. In these circumstances, events will be solicited. 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).

Solicited Adverse Events

Solicited adverse events are predefined local and systemic events for which the subject is specifically questioned. In this study, bleeding events will be solicited.

Unsolicited Adverse Events

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

12.1. Definitions

12.1.1. 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 treatment. 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 International Conference on Harmonisation [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.

A laboratory test abnormality that is considered by the investigator to be clinically relevant (eg, causing the subject to discontinue the study drug, requiring treatment, or causing apparent clinical manifestations) should be reported as an adverse event.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, 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-64179375, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

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 in Section 12.1.2, Attribution Definitions.

12.1.2. 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 drug(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 drug(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 drug(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 drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. 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).

12.2. Special Reporting Situations

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

- Overdose of a sponsor study drug. Overdose is defined as any occasion when the subject has taken or received (accidentally or intentionally or unspecified) any single dose OR a cumulative daily dose that is higher than the maximal target single dose OR a cumulative daily dose as defined in the study protocol. For apixaban, this is defined as more than 10 mg per day or more than 15 days of treatment. For JNJ-64179375, this is defined as more than the planned single-dose amount or more than 1 dose.
- 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.

12.3. Procedures

12.3.1. 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 through the Week 18 visit, 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.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

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.

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 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 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

12.3.2. 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 and Safety Report Form of the eCRF, which must be completed and reviewed 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 transmitted electronically or by facsimile (fax).

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 the Week 18, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

12.3.3. Pregnancy

All initial reports of pregnancy in partners of male subjects 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.

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

12.4. 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.

13. 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.

13.1. 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 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. 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.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drugs

JNJ-64179375 or JNJ-64179375 Placebo

The JNJ-64179375 supplied for this study is a sterile, preservative-free liquid with a concentration of 50 mg/mL of monoclonal antibody in a solution composed of 10 mM sodium phosphate, 8.5% (w/v) sucrose, 0.04% (w/v) polysorbate 20, and 10 µg/mL EDTA at a pH of 7.1. JNJ-64179375 will be provided frozen in a glass vial with an approximately 3-mL fill volume. JNJ-64179375 has a molecular mass of 149,139 Dalton for the G0F/G0F glycoform and isoelectric points, ranging from 6.1 to 6.4. The absorptivity constant for JNJ-64179375 at 280 nm was determined to be 1.37 $(mg/mL)^{-1}cm^{-1}$. It will be manufactured and provided under the responsibility of the sponsor.

Placebo infusions will be 0.9% normal saline.

Apixaban or Matching Apixaban Placebo

Apixaban will be supplied for this study as over-encapsulated 2.5-mg tablets in a red-colored, hard, gelatin capsule. The over-encapsulated tablet will be backfilled with microcrystalline cellulose to prevent the tablet from rattling in the capsule shell.

Matching apixaban placebo capsules will consist of microcrystalline cellulose within a red-colored, hard, gelatin capsule.

14.2. Packaging

JNJ-64179375 will be packaged in individual kits. Each kit will consist of 1 vial of JNJ-64179375 frozen liquid in a carton. JNJ-64179375 will not be dispensed in child-resistant packaging. It will be stored in a locked pharmacy and only dispensed after preparation for an IV infusion.

Apixaban or matching apixaban placebo will be packaged in bottles containing 30 capsules. The bottles will be child resistant.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

JNJ-64179375 must be stored at -40°C ± 10°C (-30°C to -50°C) or -70°C ± 20°C (-50°C to -90°C), and protected from light. Before use, the drug product should be diluted to the required dose strength using 0.9% normal saline. Diluted drug product for IV administration must be administered with in-line filtration.

Apixaban and matching apixaban placebo must be stored at controlled temperatures, as indicated on the product-specific labeling.

Refer to the pharmacy manual/IPPI for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. For the single IV dose of JNJ-64179375 the study drug vial(s) used to prepare the dose that will be administered to the subject must be documented in the IWRS. For oral apixaban or matching apixaban placebo, the dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented in the IWRS. 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 in the IWRS. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented in the IWRS.

Potentially hazardous materials such as used ampules, needles, syringes, vials containing hazardous liquids (this does not include the used vials of study drug), and used infusion supplies should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a 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. 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.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure for JNJ-64179375
- Laboratory manuals
- IWRS manual
- Venography manual
- eCRF manual
- Sample ICF
- IPPI
- Guidelines for Reporting Bleeding Event Verbatim Terms
- Subject contact cards (wallet card)
- Contact information page

16. ETHICAL ASPECTS

16.1. Study-Specific 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-64179375 is an investigational drug that is being developed for multiple thrombosis-mediated conditions. The nonclinical and clinical data obtained to date with JNJ-64179375 support administration of single doses in a well-controlled clinical research study. The present study is needed to support further clinical development of JNJ-64179375, 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-64179375 has not been well established as it has only been studied in a limited number of healthy male 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 study, a range of doses of JNJ-64179375 has been selected for further evaluation in Part 1 of this study. The starting dose of 0.3 mg/kg is expected to provide efficacy and be well tolerated. Subsequent dose escalation will be based on the evaluation of the observed efficacy and safety data on a regular basis (ie, every 1 to 3 weeks) by the OC, which will consist of individuals with both clinical and statistical expertise. Women will be exposed to JNJ-64179375 for the first time. The nonclinical studies did not show any difference between males and females for blood levels or tolerability of JNJ-64179375. Based on the Part 1 results, doses that are expected to provide efficacy and to be well tolerated will be selected for evaluation in Part 2. In Part 2, the IDMC will review VTE and bleeding events to closely monitor the safety of subjects participating in the study. Subjects in both parts will be monitored for 18 weeks after the single IV administration of JNJ-64179375.

The primary risk with any anticoagulant drug is the potential for bleeding events, and because JNJ-64179375 is a monoclonal antibody, infusion and hypersensitivity reactions could also be potentially observed. Based on the nonclinical evaluations of JNJ-64179375, the risk for these events is anticipated to be low (ie, all planned doses are below those shown to statistically significantly increase bleeding risk) and no cytokine release or allergic reactions have been observed in animals. In addition, subjects in the first-in-human SAD study did not experience any infusion or hypersensitivity reactions. A bleeding signal was detected at the 2.125- and 2.5-mg/kg doses in healthy male subjects. This signal consisted primarily of increased local bruising at the venipuncture and infusion sites in subjects who received JNJ-64179375 compared with placebo. The starting dose of 0.3 mg/kg in Part 1 is approximately one-seventh of this dose and was well tolerated in the SAD study. The highest planned dose (1.2 mg/kg) in Part 1 of this study is approximately 50% of the 2.125-mg/kg dose and will only be studied if lower doses are tolerated. Subjects in this study will be carefully observed for both bleeding events and infusion or hypersensitivity reactions throughout the duration of the study and management strategies for each type of event are outlined in the protocol (see Section 9.7.2.1.2, Approach to Subjects With a Bleeding Event and Section 9.7.2.2, Infusion or Hypersensitivity Reactions, respectively).

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 of the 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.[26]

There are risks associated with venipuncture and multiple blood sample collection, including prolonged bleeding due to the anticoagulant effects of JNJ-64179375. The total blood volume to be collected for safety, PK, and PD laboratory tests is approximately 95.4 mL for subjects with dense PK sampling and approximately 80.4 mL for subjects with sparse PK sampling. This is well below the standard blood donation volume for healthy donors as set forth by the World Health Organization (standard donation of 450 mL every 79 days) and is therefore considered to be acceptable for subjects following TKR surgery.[34]

16.2. Regulatory Ethics Compliance

16.2.1. 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.

16.2.2. 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)
- Investigator's Brochure (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 Investigator's Brochure 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 (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

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.

16.2.4. 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 PK, immunogenicity, and PD biomarker 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.

16.2.5. 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-64179375, to understand thrombosis, to understand differential drug responders, and to develop tests/assays related to JNJ-64179375, and VTE prophylaxis. The research may begin at any time during the study or the poststudy storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers.

16.2.6. 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 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. 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) involves 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.

17.2. Regulatory Documentation

17.2.1. 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.

17.2.2. 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

17.3. 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 and communications relating to the study will identify subjects by subject identification and date of birth (as allowed by local regulations). In cases where the subject is not randomized into the study, the date seen and date of birth (as allowed by local regulations) will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

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; drug 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.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as

the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All CRF 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 CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, 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 CRF. 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 electronic data capture (eDC) tool. If corrections to a CRF 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.

17.6. 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 IWRS data, adjudication data from the CEC, and 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. In addition, data will be reviewed centrally as described in Section 17.8, Monitoring. After upload of the data into the study database selected data will be

verified for accuracy and consistency with the data sources (refer to Section 17.8, Monitoring for further details).

17.7. 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.

17.8. 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 CRF 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 CRF 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.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the clinical trial agreement.

17.9.2. 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

17.10. 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.

17.11. Use of Information and Publication

All information, including but not limited to information regarding JNJ-64179375 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-64179375 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 cost effectiveness analyses performed will be reported in separate reports 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 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 of the availability of the final data (tables, listings, graphs), 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 Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

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.

REFERENCES

1. Baglin TP, Langdown J, Frasson R, Huntington JA. Discovery and characterization of an antibody directed against exosite I of thrombin. J Thromb Haemost. 2016;14:137-142.
2. Bornkamp B, Pinheiro J, Bretz F. Planning and analyzing dose finding experiments. http://www.cran.r-project.org/web/packages/dosefinding. Updated July 26, 2016. Accessed January 24, 2017.
3. Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics. 2005;61:738-748.
4. Buckland ST, Burnham K, Augustin NH. Model selection: an integral part of inference. Biometrics. 1997;53:603-618.
5. Büller HR, Bethune C, Bhanot S, et al; FXI-ASO TKA Investigators. Factor XI antisense oligonucleotide for prevention of venous thrombosis. N Engl J Med. 2015;372(3):232-240.
6. Cohen AT, Agnelli G, Anderson FA, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost. 2007;98:756-764.
7. Dahl OE, Borris LC, Bergqvist D, et al. International Surgical Thrombosis Forum. Major joint replacement. A model for antithrombotic drug development: from proof-of-concept to clinical use. Int Angiol. 2008;27(1): 60-67.
8. Eliquis [Summary of Product Characteristics]. Uxbridge, Middlesex, United Kingdom: Bristol-Myers Squibb/ Pfizer EEIG; 2016. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002148/human_med_001449.jsp&mid=WC0b01ac058001d124. Accessed February 9, 2017.
9. Eriksson BI, Dahl OE, Rosencher N, et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. J Thromb Haemost 5(11):2178-2185.
10. Falck-Ytter Y, Francis CW, Johanson NA, et al; American College of Chest Physicians. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2_suppl): e278S-e325S.
11. Francis CW, Davidson BL, Berkowitz SD, et al. Ximelagatran versus warfarin for the prevention of venous thromboembolism after total knee arthroplasty. A randomized, double-blind trial. Ann Intern Med. 2002;137(8):648-655.
12. Fuji T, Fujita S, Tachibana S, Kawai Y. A dose-ranging study evaluating the oral factor Xa inhibitor edoxaban for the prevention of venous thromboembolism in patients undergoing total knee arthroplasty. J Thromb Haemost. 2010;8(11):2458-2468.
13. Fuji T, Wang CJ, Fujita S, et al. Safety and efficacy of edoxaban, an oral factor Xa inhibitor, versus enoxaparin for thromboprophylaxis after total knee arthroplasty: the STARS E-3 trial. Thromb Res. 2014;134(6): 1198-1204.
14. Geerts WH (2004), Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:338S-400S.
15. Ginsberg JS, Davidson BL, Comp PC, et al. Oral thrombin inhibitor dabigatran etexilate versus North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. J Arthroplasty 24(1):1-9.
16. Hjort NL, Claeskens G. Frequentist model average estimators. J Am Stat Assoc. 2003;98:879-899.
17. Investigator's Brochure: JNJ-64179375, Edition 1. Janssen Research & Development, LLC (29 September 2016).
18. Investigator's Brochure. Addendum 1.0 to Investigator's Brochure, Edition 1.0. Janssen Research & Development, LLC (02 June 2017).
19. JCS Joint Working Group. Guidelines for the diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis (JCS 2009). Circ J. 2011;75(5):1258-1281.

20. Kearon C. Noninvasive diagnosis of deep venous thrombosis. McMaster Diagnostic Imaging Practice Guidelines Initiative. Ann Intern Med. 1998;128:663-677.

21. Lassen MR, Davidson BL, Gallus A, Pineo G, Ansell J, Deitchman D. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. J Thromb Haemost. 2007;5:2368-2375.

22. Lassen MR, Fisher W, Mouret P, et al; SAVE Investigators. Semuloparin for prevention of venous thromboembolism after major orthopedic surgery: results from three randomized clinical trials, SAVE-HIP1, SAVE-HIP2 and SAVE-KNEE. J Thromb Haemost. 2012;10(5):822-832.

23. 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.

24. Lassen MR, Raskob GE, Gallus A, et al. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet. 2010;375:807-815.

25. Pinheiro JC, Bornkamp B, Glimm E, Bretz F. Model-based dose findings under model uncertainty using general parametric models. Statistics Med. 2014;33:1646-1661.

26. Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. Arch Surg. 1972;4:134-144.

27. Schellong SM, Beyer J, Kakkar AK, et al. Ultrasound screening for asymptomatic deep vein thrombosis after major orthopaedic surgery: the VENUS study. J Thromb Haemost. 2007;5(7):1431-1437.

28. Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost. 2010;8(1):202-204.

29. Segers AE, Prins MH, Lensing AW, Buller HR. Is contrast venography a valid surrogate outcome measure in venous thromboembolism prevention studies? J Thromb Haemost. 2005;3:1099-1102.

30. Turpie AG, Lassen MR, Davidson BL, et al; RECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet. 2009;373(9676):1673-1680.

31. Verhamme P, Tangelder M, Verhaeghe R, et al; TB-402 Study Group. Single intravenous administration of TB-402 for the prophylaxis of venous thromboembolism after total knee replacement: a dose-escalating, randomized, controlled trial. J Thromb Haemost. 2011;9(4):664-671.

32. Warwick D. Prevention of venous thromboembolism in total knee and hip replacement. Circ. 2012;125: 2151-2155.

33. Winters JL. Plasma exchange: concepts, mechanisms, and an overview of the American Society for Apheresis guidelines. Hematol Am Soc Hematol Education Program. 2012;2012:7-12.

34. World Health Organization. Blood donor selection guidelines on assessing donor suitability for blood donation. Geneva: World Health Organization; 2012. http://www.ncbi.nlm.nih.gov/books/NBK138212/. Accessed 22 Sep 2016.

Attachment 1: Sample Bleeding Risk History

Family History:

1. Family history of bleeding disorder (at least one parent, grandparent, sibling or child) Yes ◯ No ◯
   If yes, what was the diagnosis? _____

Personal Lifetime History:

2. Any blood vessel aneurysms (eg, intracranial) or arteriovenous malformations? Yes ◯ No ◯
   If yes, specify diagnosis and date : _____

3. Any history of any anemia? Yes ◯ No ◯
   If yes, specify diagnosis and date: _____

4. Any history of any gastrointestinal ulcer disease? Yes ◯ No ◯
   If yes, specify diagnosis and date : _____

5. Any history of any gastrointestinal polyps? Yes ◯ No ◯
   If yes, specify diagnosis and date : _____

6. Any invasive procedures (eg, surgery, biopsy, dental extraction)? Yes ◯ No ◯
   If yes, number _____ type of procedure _____

   Any abnormal bleeding with any of the procedures? Yes ◯ No ◯
   If yes, describe and include date. _____

7. Any intracranial bleeding Yes ◯ No ◯
   If yes specify site: ◯ Subdural ◯ SAH ◯ Parenchymal Date: _____

8. Any blood in urine Yes ◯ No ◯
   If yes specify: ◯ Hematuria (Visible) ◯ Microscopic only Date: _____

9. Any muscle or joint bleeding Yes ◯ No ◯
   If yes specify: ◯ Muscle ◯ Joint Date: _____

10. Any lung bleeding Yes ◯ No ◯
    If yes specify: ◯ Blood in sputum ◯ Other, specify_____
    Date: _____

11. Any upper gastrointestinal tract bleeding Yes ◯ No ◯
    If yes specify: ◯ Hematemesis ◯ Coffee-ground emesis ◯ Melena
    Date: _____

12. FEMALES ONLY: Childbirth?
    If yes, specify if any bleeding complications? Yes ◯ No ◯

Personal History in the past 6 months:

Personal history of bleeding events in the past 6 months not involving invasive procedures (review below categories):

Gastrointestinal Bleeding-lower	No ◯	Yes ◯ →	# episodes in last 6 months: ◯ 1 ◯ 2-5 ◯ 6-12 ◯ >12 Duration of average episode: ◯ <1 min ◯ 1-5 min ◯ >5 min Type: ◯ Hemorrhoids ◯ Other, specify _____ Onset: ◯ Spontaneous ◯ After bowel movement
Nosebleeds	No ◯	Yes ◯ →	# episodes in last 6 months: ◯ 1 ◯ 2-5 ◯ 6-12 ◯ >12 Duration of average episode: ◯ <1 min ◯ 1-5 min ◯ >5 min Onset: ◯ spontaneous ◯ secondary trauma (eg, blowing nose) Resolution: ◯ Usually resolved spontaneously ◯ Required medical attention
Bruising	No ◯	Yes ◯ →	# episodes in last 6 months: ◯ 1 ◯ 2-5 ◯ 6-12 ◯ >12 Onset: ◯ With minimal or no trauma ◯ With trauma Average size: ◯ <1 cm ◯ 1-5 cm ◯ >5 cm
Oral cavity bleeding	No ◯	Yes ◯ →	# episodes in last 6 months: ◯ 1 ◯ 2-5 ◯ 6-12 ◯ >12 Type: ◯ Gums, spontaneous ◯ Gums, after brushing or flossing ◯ Other, specify _____
Bleeding from minor wounds	No ◯	Yes ◯ →	# episodes in last 6 months: ◯ 1 ◯ 2-5 ◯ 6-12 ◯ >12 Duration of average episode: ◯ <1 min ◯ 1-5 min ◯ >5 min Resolution: ◯ Usually resolved spontaneously ◯ Required medical attention
FEMALES ONLY: Dysfunctional uterine bleeding	No ◯	Yes ◯ →	# episodes in last 6 months: ◯ 1 ◯ 2-5 ◯ 6-12 ◯ >12 Duration of average episode: ◯ <1 day ◯ 1-5 days ◯ >5 days Resolution: ◯ Usually resolved spontaneously ◯ Required medical attention

Any Other Bleeding Site(s) not mentioned under lifetime or past 6 month history sections: Yes ◯ No ◯

If yes → specify site and date

Note: The final questions will be part of the eCRF. Responses to these questions will be obtained by the investigator through an interview with the subject. These responses should be reviewed and any condition for which the use of apixaban is not recommended should be considered by the investigator when determining eligibility for the study.

Attachment 2: Definitions of Bleeding Events

1. Major Bleeding in Surgical Setting[28]
    1. Fatal bleeding, and/or
    2. 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
    3. 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
    4. 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
    5. 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[23,24]

    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, CT, 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.

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 drug, 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): Gary Peters, MD

Institution: Janssen Research & Development

Signature: Gary Peters Date: 12 September 2017
(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.