Janssen Research & Development

Statistical Analysis Plan – Part 1

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

Protocol 64179375THR2001; Phase 2

JNJ-64179375

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ALT/SGPT	alanine aminotransferase
ANCOVA	analysis of covariance
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic Class
AUC	area under the curve
BMI	body mass index
CEC	Clinical Events Committee
CI	confidence interval
CL	total systemic clearance
C_{max}	maximum concentration
CRF	case report form
CRM	Continual Reassessment Method
CRNM	clinically relevant nonmajor
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
ECG	electrocardiogram
eCRF	electronic case report form
F (%)	absolute SC bioavailability
FAS	full analysis set
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IQ	interquartile
IV	intravenous
IWRS	interactive web response system
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MCP-Mod	multiple comparison procedure and modeling
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimum required dilution
MTD	maximum tolerated dose
NAb	neutralizing antibodies
OC	Operations Committee
PD	pharmacodynamic
PI	principal investigator
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Steering Committee
SD	standard deviation
SMQs	standardised MedDRA queries
TEAE	treatment-emergent adverse event
TKR	total knee replacement
Tmax	time to maximum concentration
V	volume distribution
VTE	venous thromboembolism
Vz	volume of distribution based on terminal phase
Vz/F	apparent volume of distribution based on terminal phase after extravascular administration
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This Part 1 Statistical Analysis Plan (Part 1- SAP) specifies definitions of analysis sets, key derived variables, and statistical methods for analysis of safety and efficacy for the Dose Escalation (Part 1) part of the Phase 2 study. This SAP is based on the Clinical Protocol JNJ-64179375THR2001 amendment dated September 11, 2017. Titles, mock-ups and programming instructions for all statistical outputs (tables, figures, and listings) will be provided in a separate document entitled Data Presentation Specifications (DPS). A separate Part 2 SAP will address the analyses pertaining to Part 2 of the study.

Part 1- SAP and its associated DPS will be used to generate a Topline report at the end of Part 1 of the study.

1.1. Trial 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 with a focus on evaluating major bleeding events 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 any bleeding event endpoint
- To assess the dose response of JNJ-64179375 for the prevention of total venous thromboembolism (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

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 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)

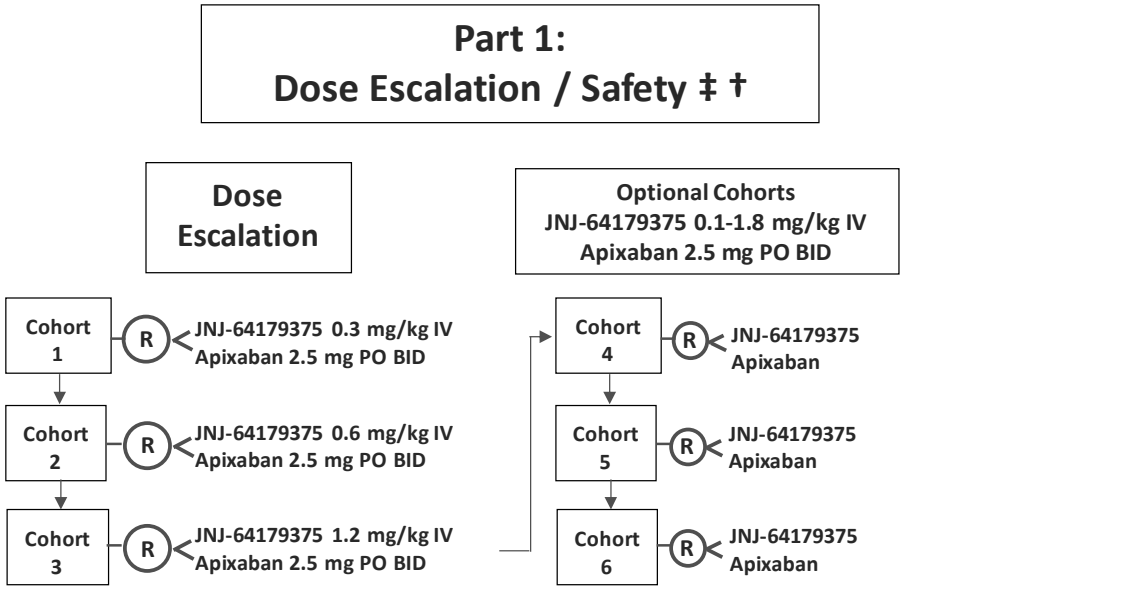
1.2. Trial Design

This is a randomized, double-blind, double-dummy, active-controlled, multicenter, dose-escalation and dose-finding study of JNJ-64179375. The study has 2 parts, dose-escalation and dose-response confirmation, 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 with respect to the selected doses in the parallel groups. Subjects will participate in either Part 1 or Part 2 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. The total duration of the subject's participation in Part 1 or Part 2 after randomization will be approximately 18 weeks.

Following primary unilateral elective TKR surgery, 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 Operations Committee (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 3weeks. Subjects enrolled in the 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 the subjects in Part 1 are expected to have completed the Day10-14 visit, an unblinded data review will be conducted by the OC, Steering Committee (SC), Independent Data Monitoring Committee (IDMC), and sponsor to determine the dose range and doses for Part 2. A schematic diagram of the study design (Part 1) is provided in Figure 1 below.

Figure 1: Schematic Overview of Part 1 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.

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

1.3. Statistical Hypotheses for Trial Objectives

The primary objective of the study in Part 1 is to assess the safety and tolerability of a range of doses of JNJ-64179375 with respect to major bleeding events for dose escalation and any bleeding events (the composite of major, clinically relevant nonmajor, and minimal bleeding events) for the selection of doses for Part 2 and hence, no statistical hypothesis will be tested. Eighty percent confidence intervals for the odd ratio of each dose over apixaban event rate with respect to major bleeding and any bleeding events (the composite of major, clinically relevant nonmajor [CRNM], and minimal bleeding events) will be constructed. For the secondary objectives, dose response of JNJ-64179375 will be assessed with respect to any bleeding events, the composite endpoint of major or clinically relevant nonmajor bleeding events, and the individual components of the any bleeding events, total VTE and individual components of total VTE events.

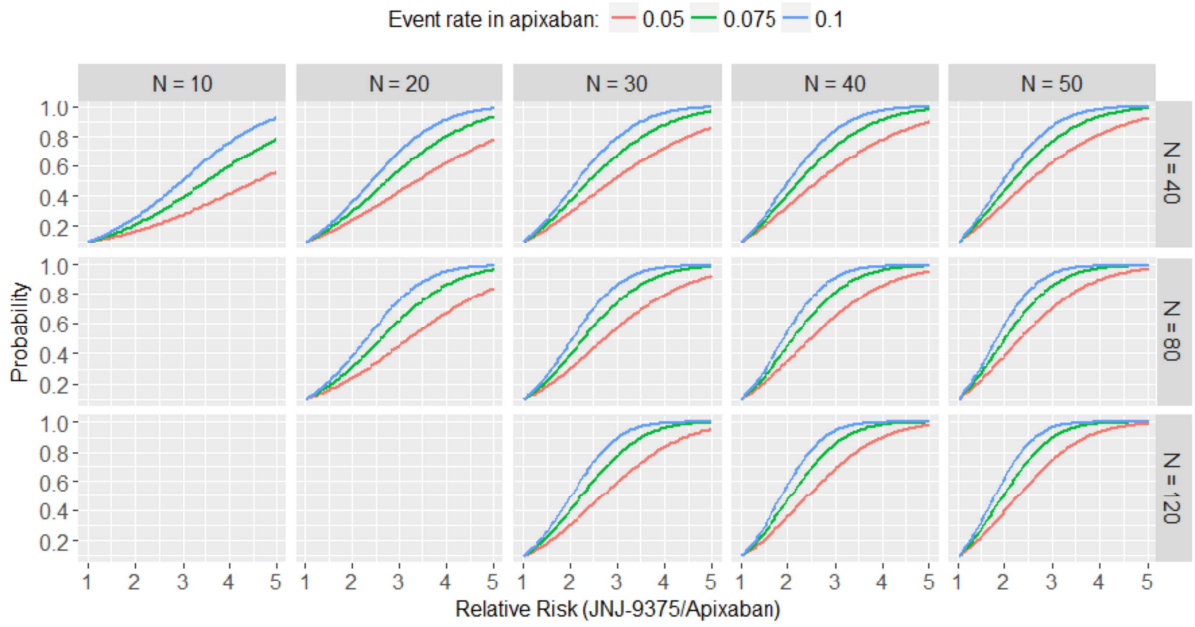
1.4. Sample Size Justification

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 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

1.5. Randomization and Blinding

Central randomization will be implemented in this study. In Part 1, within each of the planned cohorts, 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) 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 with no stratification in Part 1. 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. Separate randomization schedules will be used for Part 1 and Part 2 of the study.

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.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed at the end of the entire study. 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.

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 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.

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.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1(see section 2.6 for definition). If a subject has 2 or more actual visits in one visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint. Listed below (Table 1) are the visit windows and the target days for each visit defined in the protocol.

Table 1: Visit Windows

Parameter	Study Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
Vital signs	Screening	1	Screening	< 1	-30 to -1
	DB-Dosing	2	Baseline	<=1	1
		3	Day 2	<=2	2
		4	Day 3	<=3	3
		5	Day 7	4 to 9	7
		6	Day 10-14 (EOD/EW)	10 to 27	The midpoint in the 10 to 14-day window
	Follow-up	7	FU Week 5	28 to 55	35
		8	FU Week 10	56 to 111	70
		9	FU Week 18	112 to 140	126
Clinical Laboratory Assessments	DB-Dosing	2	Baseline	<=1	1
		3	Day 2	<=9	2
		6	Day 10-14 (EOD/EW)	10 to 27	The midpoint in the 10 to 14- day window
	Follow-up	7	FU Week 5	28 to 55	35
		9	FU Week 18	112 to 140	126
Venography of the operated leg	DB-Dosing	6	Day 10-14 (EOD/EW)	any day	10 to 14
Symptomatic thrombotic events	DB-Dosing	2	Baseline	<=1	1
		3	Day 2	<=2	2
		4	Day 3	<=3	3
		5	Day 7	4 to 9	7
		6	Day 10-14 (EOD/EW)	10 to 27	10 to 14
	Follow-up	7	FU Week 5	28 to 55	35
		8	FU Week 10	56 to 111	70
		9	FU Week 18	112 to 140	126

*Relative to Study Day 1; DB = Double-Blind; EOD = End of dosing; EW = Early withdrawal

2.2. Pooling Algorithm for Analysis Centers

All centers will be pooled. In another words, center will not be included in any statistical model.

2.3. Definition of Trial Dates

The following trial date definitions apply to Part 1 of the study.

Trial reference start date is defined as the date of randomization of the subject.

Trial reference end date is defined as the date of the last trial-related procedure for the subject; specifically, it is equal to the maximum of the following dates:

- Dates of all study-related visits (including scheduled or unscheduled visits)
- Dates of all study-related procedures, findings and events, including, but not limited to, safety and efficacy endpoint events, adverse events, concomitant medications, disposition, and death

First dose date is defined as the date on which the first dose of study drug is taken by the subject. If this date is missing or incomplete for a subject who takes study drug, the first dose date is set to the earliest logically possible date on or after randomization. More specifically, the first dose date is defined as the maximum of the randomization date and the first day of the month if only day is missing; it is defined as maximum of the randomization date and the first day of the year if day and month are missing.

Last dose date is defined as the date on which the last oral (apixaban) dose of study drug is taken by the subject. If this date is missing or incomplete for a subject who takes study drug, the last dose date is in general set to the date of the last visit at which oral (apixaban) study drug is dispensed plus the number of pills in the drug bottle(s) dispensed at that visit, but can't be later than the trial reference end date. In cases where study is still ongoing, data cut-off date will be used as the last dose date

Last outcome-evaluation date is defined as the date of the last study visit (in clinic or phone contact) while the subject is alive at which the outcome status of bleeding and efficacy endpoints is evaluated, or the date of death.

2.4. Analysis Sets

Two elements define an analysis set:

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

2.4.1. All Enrolled Analysis Set

The all enrolled analysis set is not used in this study

2.4.2. All Randomized Analysis Set

The all randomized analysis set includes all subjects who were randomized in the study.

2.4.3. Efficacy Analysis Set(s)

Remarks: - 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.

2.4.3.1. Primary Efficacy Analysis Set

Modified Intent to Treat (mITT) analysis set includes all randomized subjects with an evaluable venography assessment or a confirmed symptomatic VTE event, or any death.

2.4.3.2. Secondary Efficacy Analysis Set

Efficacy Per Protocol analysis set includes all randomized subjects with no major protocol deviations 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

Efficacy Per Protocol analysis set details: Efficacy Per Protocol analysis set includes all randomized subjects in the Up to Day 10-14 visit observation period with: -

- No major protocol deviations (see section 4.5 for major protocol deviation) → this is expected to come from Data Management
- Subject evaluable venography assessed within 24 hours after the last dose of oral study drug
  →That is, last dose date < venography assessment date ≤ last oral (Apixaban) dose date + 1 day
- Subject confirmed centrally adjudicated symptomatic VTE within 2 days of the last dose of oral study drug.
  →that is, confirmed symptomatic VTE date ≤ last oral (apixaban) dose date + 2 days
- Subject any death within 2 days of the last dose of oral study drug
  →that is, any death date ≤ last oral (apixaban) dose date + 2 days
- Subject without symptomatic VTE or death received the single complete infusion of JNJ-64179375 or at least 18 doses of oral apixaban.

  → that is, in the "Study Drug Administration" eCRF form for JNJ-64179375, "Was the Total administered?" should be equal to "Yes" or for apixaban, total # doses ≥18.

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

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

2.4.4. Safety Analysis Set

Safety analysis set includes all randomized subjects who received at least 1 dose (partial or complete) of active study drug

Safety Per Protocol analysis set includes 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 Clinical Events Committee (CEC) within 2 days of the last dose of oral study drug

Safety Per Protocol analysis set details: Safety Per Protocol analysis set includes all randomized subjects, in the Up to Day 10-14 visit observation period with:

- No major protocol deviations (see section 4.5 for major protocol deviation) → this is expected to come from Data Management
- Subject received the single complete infusion of JNJ-64179375 or at least 18 doses of oral apixaban

  → that is, in the "Study Drug Administration" eCRF form for JNJ-64179375, "Was the Total administered?" should be equal to "Yes" or for apixaban, total # doses ≥18.
- Subject bleeding event centrally adjudicated by the CEC within 2 days of the last dose of oral study drug

  → that is, CEC adjudicated bleeding event date ≤ last oral (apixaban) dose date + 2 days

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

2.4.5. Pharmacokinetics Analysis Set

The PK analysis set is defined as subjects who have received least one dose of JNJ-64179375 and have at least one valid blood sample drawn for population PK model development.

2.4.6. Immunogenicity Analysis Set

The immunogenicity analysis set is defined as all subjects who received at least one dose of JNJ-64179375 and have appropriate plasma samples for anti-JNJ-64179375 antibody detection.

2.4.7. Pharmacodynamics Analysis Set

The PD analysis set is defined as subjects who have received at least one dose of JNJ-64179375 and have at least one valid blood sample drawn for measurement.

2.5. Definition of Subgroups

No subgroup analysis is planned in Part 1.

2.6. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study agent administration or randomization date. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥date of Day 1
- Visit date - Date of Day 1, if visit date <date of Day 1

There is no 'Day 0'

2.7. Baseline and Endpoint

Baseline is defined as the last observation prior to the start of the first study agent administration or randomization date.

Endpoint is defined as the last available postbaseline result within the analysis period. Unscheduled visit results are included in this definition and will be considered as the endpoint value if the unscheduled visit result is the last postbaseline result available within the analysis period. The result refers to an event.

2.8. Imputation Rules for Missing AE Date/Time of Onset/Resolution

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the earliest study agent start.
  - The day of study agent start, if the month/year of the onset of AE is the same as month/year of the earliest study agent start date and month/year of the AE resolution date is different.
  - The day of study agent start or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the earliest study agent start date and month/year of the AE resolution date are same.
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the earliest study agent start date,
  - Month and day of the earliest study agent start date, if this date is in the same year that the AE occurred,
  - Last day of the year if the year of the AE onset is prior to the year of the earliest study agent start date,
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

AE onset/resolution dates with missing times will be imputed as follows:

- A missing time of onset of an adverse event will be set to the earlier of:
  - 00:01 as long as the onset date is after the study agent start date,
  - The time of the study agent start if this is the same day the AE occurred.
- The missing time of resolution of an adverse event will be set to 23:59.

If a missing time is associated with a partial or missing date, the date will be imputed first prior to imputing the time.

Remarks: Imputation rules for missing Event dates will follow similar rules as for AEs.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

There is no interim analysis in Part 1, however, there is an ongoing safety data monitoring and dose escalation/selection data review meeting by an OC, which includes the SC and IDMC chairpersons.

3.1. Operations Committee Review

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, including the dose-escalation decision guidelines are described in the OC charter.

The OC Charter could be revised; therefore, the Charter should be referenced for the most current information since this SAP may not be updated with specific OC changes.

A separate SAP will not be provided for the operations committee review.

During the beginning of enrollment, the OC will be provided and review investigator reported safety and efficacy events. As CEC adjudicated data is available this will also be provided to the committee for review.

3.1.1. Dose Escalation Decision Guidelines

OC will review data in an ongoing basis and make a dose escalation decision with intention to study at least 25 subjects at the current dose before escalating to the next higher dose. Dose escalation will be based on the totality of both efficacy and safety data coming from the current and previous cohorts.

Suggested Stopping criteria: meeting any of the following criteria in the highest dose studied could prohibit further dose escalation

- The lower bound of 1-sided 90% CI for major bleeding endpoint is greater than 2%, 3% or 4%.

The following thresholds for major bleeding, based on these rates, will be referenced and are suggested as a guideline when making dosing decisions. Bleeding that is high enough that it crosses one of the thresholds may require stopping dose escalation.

Table 2 can also be used as a suggested threshold for escalating the dose based on the composite major VTE endpoint (proximal DVT, non-fatal PE or any death).

Table 2: Suggested Threshold to Stop Dose Escalation Based on Number of Subjects with Major Bleeding Events

	Number of Subjects with Major Bleeding Events		
Number of Events	Reference Rate: 2%	Reference Rate: 3%	Reference Rate: 4%
2	Up to 26 (7.7%)	Up to 17 (11.8%)	Up to 13 (15.4%)
3	Up to 55 (5.5%)	Up to 37 (8.1%)	Up to 28 (10.7%)
4	Up to 87 (4.6%)	Up to 58 (6.9%)	Up to 44 (9.1%)
5	Up to 122 (4.1%)	Up to 81 (6.2%)	Up to 61 (8.2%)
6	Up to 158 (3.8%)	Up to 105 (5.7%)	Up to 79 (7.6%)
7	Up to 195 (3.6%)	Up to 130 (5.4%)	Up to 98 (7.1%)
8	Up to 233 (3.4%)	Up to 156 (5.1%)	Up to 117 (6.8%)
9	Up to 272 (3.3%)	Up to 182 (4.9%)	Up to 137 (6.6%)
10		Up to 208 (4.8%)	Up to 156 (6.4%)
11		Up to 235 (4.7%)	Up to 177 (6.2%)
12		Up to 262 (4.6%)	Up to 197 (6.1%)

*Smallest number of events that result in the lower bound of the one-sided 90% confidence interval exceed thresholds.

- The lower bound of 1-sided 90% CI for the difference in any bleeding event rate between the JNJ-64179375 arm and the apixaban arm is greater than 0.

Table 3: Examples Where the Lower Bound of 1-sided 90% CI for the Between-Treatment Difference is Greater than 0

JNJ-64179375	Apixaban	Lower Bound
8/25 (32%)	1/10 (10%)	1%
5/25 (20%)	1/20 (5%)	2%
9/50 (18%)	3/40 (7.5%)	1%

- The lower bound of 1-sided 90% CI for the difference in the composite of major and clinically relevant nonmajor (CRNM) bleeding event rate between the JNJ-64179375 arm and the apixaban arm is greater than 0.

Continual Reassessment Method (CRM), a model based approach commonly used in oncology dose escalation study to determine Maximum Tolerated Dose (MTD), will also be employed to predict event rates in next higher dose to guide the dose escalation process.

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.

The following sections describe details of the analysis and summary of Part 1 data.

4. SUBJECT INFORMATION

The number of subjects in each analysis set will be summarized and listed by treatment group, combined JNJ-64179375 treatment group, and overall. In addition, the distribution of subjects by, country, and site ID will be presented unless otherwise noted.

4.1. Demographics and Baseline Characteristics

Table 4 presents a list of the demographic variables that will be summarized by treatment group, combined JNJ-64179375 treatment group, and overall for the safety analysis set(s).

Table 4: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m2)	
Categorical Variables	
Age (18-<50, 50 - <65, 65 - <75, ≥ 75)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female, undifferentiated)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI ([underweight <18.5 kg/m2, normal 18.5-<25 kg/m2, overweight 25-<30 kg/m2, obese ≥30 kg/m2])	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

The following analyses sets (Table 5) will be summarized by treatment group.

Table 5: Analysis Sets

Categorical Variables	
Efficacy (mITT, Per-protocol)	Frequency distribution with the number and percentage of subjects in each category.
Safety* (Safety, Per-protocol)	
All Randomized	All randomized will only be used to summarize subject disposition

*Bleeding event analysis will be based on both safety and per-protocol analysis sets; Adverse events will be based on safety analysis set only

4.2. Disposition Information

Screened subjects and reason for screen failures will be summarized overall at end of Part 1.

The number of subjects in the following disposition categories will be summarized throughout the study by treatment group and overall:

- Subjects randomized
- Subjects receiving study agent
- Subjects completing the study
- Subjects who discontinued study agent
- Reasons for discontinuation of study agent
- Subjects who terminated study prematurely
- Reasons for termination of study

The above categories will include summaries over the time points:

- Day 1 to Day 10-14;
- > Day 10-14 to Week 18;

Listings of subjects will be provided for the following categories:

- Subjects who discontinued study agent
- Subjects who terminated study prematurely
- Subjects who were unblinded during the study period
- Subjects who were randomized yet did not receive study agent.

4.3. Treatment Compliance

-Study agent compliance will be calculated as follows:

a) For oral apixaban or matching apixaban placebo

Study agent compliance (%) = (actual number of tablets taken/total number of tablets supposed to be taken) x100.

b) For single IV dose of JNJ-64179375 or saline only IV infusion

Study agent compliance (%) = (actual total volume through the IV (mL) administered / total amount through the IV (mL) supposed to be administered) x100.

Remarks: Based on the protocol, the denominators in a) and b) above are expected to be documented in IWRS.

The reasons for not taking the total dose through the IV (mL) will be summarized. The categories for the reasons are:

- Adverse event,
- IV access issue, and
- Other.

The anatomical location of the IV dose administration (Right arm, Left arm) will also be summarized.

4.4. Extent of Exposure

The number and percentage of subjects who receive study agent will be summarized by treatment group

Descriptive statistics for study agent duration (N, mean, SD, median, and range (minimum, maximum) will be presented by treatment group for the safety analysis set.

Duration of exposure for apixaban will be summarized in the following duration categories <1, 2 - <5, 5- <10, 10- <15, ≥ 15 days by treatment group.

Study agent duration is defined as (date of last oral (apixaban) dose of study agent – date of first dose of study agent) +1.

Total dose days of exposure is defined as the total number of days that study agent was administered to the subject (excluding days of study agent interruption).

The total number of dose administrations received will be summarized in the following count categories 1, 2 - <5, 6- <9, 10- <15, 16- <20, 20- <29, >= 29 by treatment group.

Descriptive statistics will be presented for the following parameters:

- Number of administrations

4.5. Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical study. Subjects with major protocol deviations will be identified prior to database lock and the subjects with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Others

4.6. Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study agent. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study agent, including those that started before and continue on after the first dose of study agent.

Summaries of concomitant medications will be presented by ATC term and treatment group. The proportion of subjects who receive each concomitant medication will be summarized as well as the proportion of subjects who receive at least one concomitant medication. In addition, concomitant medications of special interest will be presented. These include tranexamic acid (TXA), antiplatelet therapies, anticoagulant therapies, and nonsteroidal anti-inflammatory drug (NSAIDs). See Attachment 1 for Concomitant medications of special interest WHO categories.

Prior medications will be summarized by treatment group and ATC term.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

As stated in section 1.3 above, no statistical hypothesis will be tested in Part 1 of the study. However, for the OC review of data on an ongoing basis and for making dose escalation decisions, suggested stopping criterion are based on lower bounds of one-sided 90% confidence intervals. These lower bounds when crossed indicate JNJ-64179375 dose(s) not being favorable with respect to the endpoints considered.

For the unblinded data review planned after all subjects are expected to have completed the Day 10-14 visit for Part 1one-sided 90% confidence intervals will be used for comparing JNJ-64179375 dose(s) with apixaban.

5.1.2. Data Handling Rules

5.2. Primary Efficacy Endpoint(s)

The primary efficacy endpoint is total VTE.

Note: - The focus of Part 1 will be primarily dose escalation based on safety. Total VTE in Part 1 of the study is used to address the secondary objective of assessing the dose response of JNJ-64179375 for the prevention of total VTE.

5.2.1. Definition

Total VTE is 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.

➔ Total VTE = Proximal DVT (Asymptomatic or Symptomatic) + Distal DVT (Asymptomatic or Symptomatic) + Nonfatal PE + Any death

The primary window for analysis of Total VTE is the up to Day 10-14 visit observation period.

The following maps the locations in eCRF of the investigator reported components needed in the definition of total VTE:

Total VTE Component	eCRF Form name (s)	Comments
Symptomatic DVT (Proximal or Distal)	Suspected Symptomatic Deep Vein Thrombosis	In the opinion of the investigator, does this event meet the protocol definition of Symptomatic Deep Vein Thrombosis? YES
Asymptomatic DVT (Proximal or Distal)	Planned Day 10-14 Venography	Proximal clot or Distal clot
Nonfatal PE	Suspected Symptomatic Pulmonary Embolism & Death	Suspected symptomatic PE & Alive
Death	Death	

5.2.2. Estimand

Population: subjects undergoing primary unilateral elective TKR surgery

Endpoint: Total VTE

Measure of Intervention: the effect of the initially randomized treatment that would have been observed had all subjects remained on their treatment throughout the DB dosing phase.

5.2.3. Analysis Methods

a) In support of the dose escalation decision within Part 1, the following will be summarized.

- The number of subjects with Total VTE, and the secondary endpoint Major VTE (see section 5.3.1 for definition) up to Day 10-14 visit observation period and the corresponding lower bound of 1-sided 90% confidence interval for dose escalation by cohort/dose. If the computed lower bound based on any or both observed Total VTE, Major VTE rates, in the highest JNJ-64179375 dose studied, is greater than a predefined threshold then it could signal that further dose escalation be considered if there is no safety issue at the dose considered.

  The lower bound of 1-sided 90% confidence interval used for comparison to the threshold is a one sample CI, which is equivalent to a lower bound of 2-sided 80% CI., that can be obtained using the Exact method in PROC FREQ (in SAS).

  Note that the suggested guidelines in Table 2 in section 3.1.1 provide similar information in terms of number of Major VTE events for the thresholds 2%, 3% or 4%.

- The number of subjects with Total VTE, Major VTE up to Day 10-14 visit observation period and the corresponding lower bound of 1-sided 90% confidence interval for the between JNJ-64179375 dose and apixaban (or cumulative apixaban beginning from cohort 1) treatment difference of event rate for dose escalation by cohort/dose.

  The lower bound of 1-sided 90% confidence interval used for comparison to the threshold (0) is a two sample CI will be based on Miettinen and Nurminen (1985) method and will be computed in SAS following the closed form formulas for the method (Garner W). This method, unlike the most widely known Wald method (ie, normal approximation), does not produce undesirable results in extreme cases (eg, when the proportions are near 0 or 1).

Summaries from the above, will be presented as side by side for CEC adjudicated, investigator reported and best available Total VTE, Major VTE events, where best available is always CEC adjudicated if a subject has both CEC adjudicated and investigator reported events.

- Continual Reassessment Method (CRM), a model based approach commonly used in oncology dose escalation study to determine MTD, will also be employed to predict event rates in next higher dose to guide the dose escalation process.

b) For the unblinded data review planned after all subjects are expected to have completed the Day 10-14 visit for Part 1, the following summary and analysis will be performed.

- Incidence of total VTE, major VTE with associated component events up to day 10-14 visit observation period will be summarized by treatment group for the modified ITT (mITT) analysis set. 90% confidence intervals for the odd ratio of each JNJ-64179375

dose over apixaban event rate with respect to Total VTE and Major VTE events will also be constructed.

- Dose response of JNJ-64179375 with respect to total VTE will be assessed using a two-stage generalized least squares approach model fitting methodology (Pinheiro el al, Stat in Med, 2013). That is, in the first stage, ANOVA-type model to the binary, total VTE data, based on the logistic regression model are fit using dose as factor. In the second stage, various candidate models (on logit scale) are fit using the estimates (from first stage) employing the Multiple Comparisons and Modeling (MCPMod) approach to the dose levels and associated variance-covariance matrix estimates from stage 1. The following candidate models will be considered: linear, emax, exponential, logistic and sigEmax. Dose-response effect are tested using a model-based multiple contrast test to select one (or several) model(s) from the significant shapes. The best fitting model to the data are picked using either the gAIC or aveAIC model selection criterion. The model with the smallest gAIC or aveAIC value is considered to fit the data best. Plots of the observed data and model fit including the 95% confidence intervals of the fitted lines will be presented using response rate on the y-axis and dose on the x-axis

5.3. Major Secondary Endpoints

- Major VTE
- All individual components of the primary efficacy endpoint
    - Proximal DVT
        - Asymptomatic
        - Symptomatic
    - Distal DVT
        - Asymptomatic
        - Symptomatic
    - Nonfatal PE
    - Any death

5.3.1. Definition

Major VTE is defined as the composite of proximal DVT (asymptomatic confirmed by venography assessment of the operated leg or objectively confirmed symptomatic), nonfatal PE, or any death

➔ Major VTE = Proximal DVT (Asymptomatic or Symptomatic) + Nonfatal PE + Any death

The following maps the locations in eCRF of the investigator reported components needed in the definition of Major VTE:

Major VTE Component	eCRF Form name(s)	Comments
Symptomatic DVT (Proximal)	Suspected Symptomatic Deep Vein Thrombosis	In the opinion of the investigator, does this event meet the protocol definition of Symptomatic Deep Vein Thrombosis? → YES & Proximal
Asymptomatic DVT (Proximal)	Planned Day 10-14 Venography	Proximal clot
Nonfatal PE	Suspected Symptomatic Pulmonary Embolism & Death	Suspected symptomatic PE & Alive
Death	Death	

5.3.2. Analysis Methods

See section 5.2.3 above for major VTE summary and analysis.

5.4. Other Efficacy Variable(s)

The following are listed as part of exploratory endpoints in the protocol:

- Other thrombotic events
  - Myocardial Infarction (MI)
  - Ischemic stroke
  - Peripheral arterial embolism

5.4.1. Definition

The following maps the location in eCRF of other efficacy variables

Other Efficacy Variables	eCRF Form name(s)	Comments
Myocardial Infarction (MI)	Suspected Myocardial Infarction/ Unstable Angina	In the opinion of the investigator, does this event meet the protocol definition of Myocardial Infarction → YES
Ischemic stroke	Suspected Stroke / Transient Ischemic Attack (TIA)	In the opinion of the investigator, does this event meet the protocol definition of Stroke → YES

Peripheral arterial embolism	Suspected Peripheral Artery Embolism	In the opinion of the investigator, does this event meet the protocol definition of Peripheral Artery Embolism? → YES

5.4.2. Analysis Methods

Incidence of Myocardial Infarction (MI), Ischemic stroke and Peripheral arterial embolism up to day 10-14 visit observation period will be summarized by treatment group for the modified ITT (mITT).

6. SAFETY

6.1. Primary Safety (Bleeding) Endpoint

The primary safety endpoint is any bleeding event

6.1.1. Definition

Any bleeding event is defined as the composite of major, CRNM, and minimal bleeding events

- Any bleeding = Major + CRNM + Minimal

The primary window for analysis of any bleeding event is the up to Day 10-14 visit observation period.

The following maps the location in eCRF of the investigator reported components needed in the definition of any bleeding:

Any bleeding	**eCRF Page # (s)**	**Comments**
Bleeding Category	Bleeding Event	Classify the bleeding category as defined in Attachment 2 of the protocol: • Major Bleeding in Surgical Setting • Clinically Relevant Nonmajor Bleeding • Minimal Bleeding

6.1.2. Safety (Bleeding) Analysis Methods

a) In support of the dose escalation decision within Part 1, the following will be summarized.

- The number of subjects with Major bleeding up to Day 10-14 visit observation period and the corresponding lower bound of 1-sided 90% confidence interval for dose escalation by cohort/dose. If the computed lower bound based on the observed rates, in the highest JNJ-64179375 dose studied, is greater than a predefined threshold, e.g., 2%, 3% or 4%, then it could signal that further dose escalation be prohibited.

The lower bound of 1-sided 90% confidence interval used for comparison to the threshold is a one sample CI, which is equivalent to a lower bound of 2-sided 80% CI., that can be obtained using the Exact method in PROC FREQ (in SAS).

- The number of subjects with Any bleeding up to Day 10-14 visit observation period and the corresponding lower bound of 1-sided 90% confidence interval for the between JNJ-64179375 dose and apixaban (or cumulative apixaban beginning from cohort 1) treatment difference of event rate for dose escalation using greater than zero threshold by cohort/dose.

  The lower bound of 1-sided 90% confidence interval used for comparison to the threshold (0) is a two sample CI will be based on Miettinen and Nurminen (1985) method and will be computed in SAS following the closed form formulas for the method (Garner W). This method, unlike the most widely known Wald method (ie, normal approximation), does not produce undesirable results in extreme cases (eg, when the proportions are near 0 or 1).

Summaries from the above, will be presented as side by side for CEC adjudicated, investigator reported and best available, where best available is always CEC adjudicated if a subject has both CEC adjudicated and investigator reported events.

- Continual Reassessment Method (CRM), a model based approach commonly used in oncology dose escalation study to determine MTD, will also be employed to predict event rates in next higher dose to guide the dose escalation process.

b) For the unblinded data review planned after all subjects are expected to have completed the Day 10-14 visit for Part 1, the following summary and analysis will be performed.

- Incidence of Any bleeding with associated component events will be summarized by treatment group for the safety analysis set. 90% confidence intervals for the odd ratio of each JNJ-64179375 dose, as well as combined JNJ-64179375 doses, over apixaban event rate with respect to Any bleeding and its associated component events will also be constructed.

- Dose response of JNJ-64179375 with respect to Any bleeding will be assessed using a two-stage generalized least squares approach model fitting methodology (Pinheiro el al, Stat in Med, 2013). That is, in the first stage, ANOVA-type model to the binary, Any bleeding data, based on the logistic regression model are fit using dose as factor. In the second stage, various candidate models (on logit scale) are fit using the estimates (from first stage) employing the multiple comparison and modeling (MCP-Mod) approach to the dose levels and associated variance-covariance matrix estimates from stage 1. The following candidate models will be considered: linear, emax, exponential, logistic and sigEmax. Dose-response effect are tested using a model-based multiple contrast test to select one (or several) model(s) from the significant shapes. The best fitting model to the data are picked using either the gAIC or aveAIC model selection criterion. The model

with the smallest gAIC or aveAIC value is considered to fit the data best. Plots of the observed data and model fit including the 95% confidence intervals of the fitted lines will be presented using response rate on the y-axis and dose on the x-axis.

6.2. Major (Key) Secondary Safety Endpoints

All individual components of the primary safety endpoint

- Major bleeding,
- Clinically relevant nonmajor bleeding,
- Minimal bleeding

Composite of major and clinically relevant nonmajor bleeding

6.3. Other Secondary Safety Endpoints

Any wound or joint complication in the operated leg

The following maps the location in eCRF of wound or joint complication in the operated leg

Wound or Joint Complications	eCRF Page # (s)	Comments
Wound or Joint Complications	Wound or Joint Complications	

Table 6 presents layout how Wound or Joint Complications will be summarized by treatment group for the safety analysis set(s).

Table 6: Wound or Joint Complications

Wound Complications for the operated leg/ surgical site (a)	Summary Type
Infection	Use the analogy of AE summary by SOC and Preferred term where (a) and (b) play the role of SOC and items underneath play the role of Preferred term Provide in the summary, the number of subjects with any wound or joint complication in the operated leg .
Poor Wound Healing	
Edema	
Erythema	
Other	
Joint Complications (b)	
Infection	
Loosening	
Instability	
Periprosthetic fracture	
Abnormal joint pain	
Other	

6.4. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study agent through the day of last dose to up to last contact date is considered to be treatment emergent. If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study agent based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and 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.

Summary tables will be provided for:

- All AEs and TEAEs
- All Serious AEs (SAEs) and TESAEs
- AEs leading to discontinuation of study agent/termination of study participation
- TEAEs by severity
- TEAEs by relationship to study agent

In addition to the summary tables, listings will be provided for subjects who:

- Had SAEs
- Had AEs leading to discontinuation of study agent

Incidence of other treatment-emergent adverse events of special interest will be summarized.

As per protocol, adverse events of special interest include 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. Subjects with adverse events of special interest may be counted or listed using MedDRA SMQs (eg, hemorrhage excluding laboratory terms SMQ).

The following maps the location in eCRF of adverse events of special interest

Adverse events of special interest	**eCRF Form names(s))**	**Comments**
Specify AE special interest type	Adverse Events/Serious AEs	

Deaths will be displayed by actual treatment received. Frequencies for the following parameters will be included in the summary table:

- Number of subjects who died
- Cause of death
- Relationship to study agent (yes/no)

A listing of subjects who died will be provided.

6.5. Clinical Laboratory Tests

All clinical laboratory tests will be displayed for the subjects included in the safety analysis set by visit and treatment group.

Laboratory assessments (hematology, chemistry and urinalyses) were made at Day 0, Day 2, Day 10-14, Week 5 and Week 18 Visits.

Descriptive statistics will be presented for all chemistry, hematology, and urinalysis laboratory tests at scheduled time points.

Change from baseline to scheduled time point will be summarized for chemistry, hematology, and urinalysis tests and displayed by visit and treatment group.

Number and percentage of subjects with postbaseline clinically important laboratory values and/or markedly abnormal postbaseline values will be presented by visit and treatment group.

The clinically important laboratory findings to be reported are described below:

- AST (U/L): 3x ULN
- ALT (U/L): 3x ULN

Markedly abnormal laboratory findings to be reported are described below:

- AST (U/L): 5x ULN
- ALT (U/L): 5x ULN
- Hgb < 80 g/L
- Plt < 50 K
- Cr > 176.8 µmol/L

A listing of clinically important and markedly abnormal laboratory values will be provided.

Shift tables will be provided summarizing, by treatment group, the shift in laboratory values from baseline to each scheduled time point with respect to abnormality criteria (low, normal, high).

6.6. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including temperature, weight, pulse, blood pressure (systolic and diastolic), will be summarized at each assessment time point. Changes from Baseline will be summarized for the Up to Day 10-14 visit. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented. A listing of subjects with treatment-emergent clinically important vital signs will be presented,

Incidence of treatment-emergent clinically important abnormalities in vital signs while on treatment, as defined in Table 7, will be summarized for subjects who had a baseline assessment and at least one postbaseline assessment for that vital sign.

Table 7: Clinically Important Abnormalities in Vital Signs

Vital Sign	Criteria
Pulse	>120 bpm and with >30 bpm increase from baseline
	<50 bpm and with >20 bpm decrease from baseline
Systolic blood pressure	>180 mm Hg and with >40 mm Hg increase from baseline
	<90 mm Hg and with >30 mm Hg decrease from baseline
Diastolic blood pressure	>105 mm Hg and with >30 mm Hg increase from baseline
	<50 mm Hg and with >20 mm Hg decrease from baseline
Temperature	>38°C and with ≥1°C increase from baseline
Weight	increase 10% kg from baseline
	decrease10% kg from baseline

6.7. Electrocardiogram

A 12-lead ECG will be performed during screening. No summary is planned.

7. PHARMACOKINETICS/PHARMACODYNAMICS

Samples for analysis of JNJ-64179375 plasma concentration and PD markers will be collected for all subjects over time as specified in the Time and Events Schedule in the protocol, however will only be analyzed for subjects randomly assigned to JNJ-64179375. All PK and PD samples will be sent to a central laboratory

7.1. Pharmacokinetics

PK samples will be analyzed by Janssen Laboratories, Springhouse, PA, USA. Plasma samples will be analyzed to determine concentrations of JNJ-64179375 using a validated, selective, and sensitive immunoassay method (lower limit of quantification 0.01 µg/mL). 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.

PK analyses will be performed on the PK analysis set defined as subjects who have received at least one dose of JNJ-64179375 and have at least one valid blood sample drawn for PK analysis and whose PK profiles contributes to the development of a population PK model for JNJ-64179375 in this patient population. All subjects and samples excluded from the analysis will be clearly documented.

If sufficient data are available, then population PK analysis using plasma concentration-time data of JNJ-64179375 will be performed using nonlinear mixed-effects modeling. PK data may be displayed graphically. Details will be given in a population PK analysis plan and the results of the analysis will be presented in a separate report.

Efficacy endpoints will be cross tabulated based on quartiles of plasma JNJ-64179375 concentration.

7.2. Immune Response

This will be done at end of part 2 so none for part 1.

7.3. Pharmacodynamics

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. Another sample will be collected on Day 10-14 visit window. 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. All assays will be performed by a central specialty laboratory (Esoterix , Englewood , CO, USA) .

7.4. Pharmacokinetic/Pharmacodynamic Relationships

In the Phase 1 single ascending dose study, the 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. Thus, the relationship between PK and PD will be explored further to determine the nature of the relationship by mixed effects models (linear or non-linear) utilizing the data from this study.

PD Analysis Sets will be respectively used for summaries PD parameters. The details of PK and PD analysis plan are to be provided as a separate document.

8. HEALTH ECONOMICS

This section is not applicable for Part 1 and will only be considered in Part 2.

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ATTACHMENTS

ATTACHMENT 1 Medications of Special Interest
Concomitant medications of special interest are defined as follows:

Concomitant Medication Special Interest Category	**Standard ATC Group Name**	ATC Group Code	**Standard Medication Name**	ATC code
ANTITHROMBOTIC AGENTS	Heparin group	B01AB	heparin	B01AB01
			antithrombin III	B01AB02
			dalteparin	B01AB04
			enoxaparin	B01AB05
			nadroparin	B01AB06
			parnaparin	B01AB07
			reviparin	B01AB08
			danaparoid	B01AB09
			tinzaparin	B01AB10
			sulodexide	B01AB11
			bemiparin	B01AB12
	Platelet aggregation inhibitors excl. heparin	B01AC	clopidogrel	B01AC04
			ticlopidine	B01AC05
			acetylsalicylic acid	B01AC06
			dipyridamole	B01AC07
			carbasalate calcium	B01AC08
			iloprost	B01AC11
			abciximab	B01AC13
			eptifibatide	B01AC16
			tirofiban	B01AC17
			treprostinil	B01AC21
			prasugrel	B01AC22
			cilostazol	B01AC23
			ticagrelor	B01AC24
			cangrelor	B01AC25
	Enzymes	B01AD	streptokinase	B01AD01
			alteplase	B01AD02
			anistreplase	B01AD03
			urokinase	B01AD04
			reteplase	B01AD07
			drotrecogin alfa (activated)	B01AD10
			tenecteplase	B01AD10
	Direct thrombin inhibitors	B01AE	desirudin	B01AE01
			lepirudin	B01AE02
			argatroban	B01AE03

Concomitant Medication Special Interest Category	**Standard ATC Group Name**	ATC Group Code	**Standard Medication Name**	ATC code
			melagatran	B01AE04
			ximelagatran	B01AE05
			bivalirudin	B01AE06
			dabigatran etexilate	B01AE07
	Direct factor Xa inhibitors	B01AF	rivaroxaban	B01AF01
			apixaban	B01AF02
			edoxaban	B01AF03
	Other antithrombotic agents	B01AX	defibrotide	B01AX01
			fondaparinux	B01AX05
VITAMIN K AND OTHER HEMOSTATICS	Local hemostatics	B02BC	thrombin	B02BC06
ANTIFIBRINOLYTICS	Amino acids	B02AA	tranexamic acid	B02AA02
			aminocaproic acid	B02AA01
NASAL DECONGESTANTS FOR SYSTEMIC USE	Sympathomimetics	R01BA	phenylpropanolamine	R01BA01
			pseudoephedrine	R01BA02
			phenylephrine	R01BA03
			phenylpropanolamine, combinations	R01BA51
			pseudoephedrine, combinations	R01BA52
OTHER ANALGESICS AND ANTIPYRETICS	Salicylic acid and derivatives	N02BA	carbasalate calcium	N02BA15
			carbasalate calcium combinations excl. psycholeptics	N02BA65
INTESTINAL ANTIINFLAMMATORY AGENTS	Aminosalicylic acid and similar agents	A07EC	sulfasalazine	A07EC01
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	M01A	Butylpyrazolidines	M01AA
			Acetic acid derivatives and related substances	M01AB

Concomitant Medication Special Interest Category	**Standard ATC Group Name**	ATC Group Code	**Standard Medication Name**	ATC code
			Oxicams	M01AC
			Propionic acid derivatives	M01AE
			Fenamates	M01AG
			Coxibs	M01AH
			Other antiinflammatory and antirheumatic agents, non-steroids	M01AX
	ANTIINFLAMMATORY /ANTIRHEUMATIC AGENTS IN COMBINATION	M01B	Antiinflammatory/antirheumatic agents in combination with corticosteroids	M01BA
			Other antiinflammatory/antirheumatic agents in combination with other drugs	M01BX