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**Janssen Research & Development**

**Statistical Analysis Plan**

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

**Protocol 70033093THR2001; Phase II**

**JNJ-70033093**

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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

| | |
|---|---|
| AE | adverse event |
| ALT/SGPT | alanine aminotransferase |
| APAC | Asia Pacific |
| AST/SGOT | aspartate aminotransferase |
| ATC | anatomic and therapeutic class |
| BID | twice daily |
| BMI | body mass index |
| CEC | Clinical events committee |
| CI | confidence interval |
| CRF | case report form |
| CRNM | clinically relevant non-major |
| CSR | Clinical Study Report |
| CV | coefficient of variation |
| DPS | Data Presentation Specifications |
| DVT | Deep vein thrombosis |
| (e)CRF | (electronic) case report form |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| ICH | International Conference on Harmonization |
| IQ | interquartile |
| IWRS | interactive web response system |
| LATAM | Latin America |
| MCP-Mod | multiple comparison procedures and modeling |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MINS | Myocardial injury in noncardiac surgery |
| (m)ITT | (Modified) intent-to-treat |
| N | Total number |
| NA | North America |
| OC | Operations committee |
| PD | Pharmacodynamic |
| PE | pulmonary embolism |
| PI | principal investigator |
| PK | pharmacokinetic(s) |
| PP | per protocol |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | standard deviation |
| SDS | Secure Data Supplier |
| SMQs | standardized MedDRA queries |
| TEAE | treatment-emergent adverse event |
| TKR | Total knee replacement |
| VTE | Venous thromboembolism |
| WHO | World Health Organization |
| WHO-DD | World Health Organization Drug Dictionary |

# 1. INTRODUCTION

This Statistical Analysis Plan (SAP) specifies definitions of analysis sets, key derived variables, and statistical methods for analysis of efficacy and safety for the Phase 2 study 70033093THR2001. This SAP is based on the Clinical Protocol 70033093THR2001 amendment 1 dated September 10, 2019. Titles, mock-ups and programming instructions for all statistical outputs (tables, figures and listings) will be provided in a separate document entitled Data Presentation Specifications (DPS). This SAP and its associated DPS will be used to generate a topline report and a Clinical Study Report (CSR) after database lock.

## 1.1. Trial Objectives

***Primary Objective***

- To determine the efficacy of JNJ-70033093 in preventing total VTE events (proximal and/or distal DVT [asymptomatic confirmed by venography assessment or objectively confirmed symptomatic], nonfatal PE, or any death) during the treatment period

***Secondary Objectives***

- To assess the dose-response of JNJ-70033093 for the occurrence of the endpoint of any bleeding events during the treatment period
- To determine the efficacy of JNJ-70033093 in preventing total VTE events during the full study period
- To assess the dose-response of JNJ-70033093 for the rate of any bleeding throughout the full study period
- To assess the dose-response of JNJ-70033093 for the prevention of major VTE (death, asymptomatic or symptomatic proximal DVT or nonfatal PE) during the treatment period and throughout the full study period
- To assess the effect of individual doses of JNJ-70033093 compared with enoxaparin for both efficacy and safety endpoints
- To compare the effect of JNJ-70033093 with enoxaparin for the individual components of the total VTE endpoint
- To assess the PK of JNJ-70033093 in men and women undergoing primary unilateral TKR surgery and the relation of these measures to efficacy and safety endpoints (e.g., exposure-response analyses)

***Exploratory Objectives***

- To evaluate PD to assess its relationships to PK and the relation of these measures to efficacy and safety endpoints (e.g., exposure-response analyses).
- To evaluate exploratory biomarkers to assess their relationship to the probability of total VTE during the treatment period.
- To explore the presence and incidence of asymptomatic myocardial injury in noncardiac surgery (MINS) as it relates to total knee arthroplasty.

The full study period and the treatment period are defined in Section 2.3.

## 1.2. Trial Design

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

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

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

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

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

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

Subjects will return to the study site 6 weeks after the TKR surgery for study-related evaluations and procedures as described in the Schedule of Activities. Safety evaluations will include the monitoring of all adverse events (AE), including nonserious adverse events, serious adverse events (SAE), adverse events of interest (i.e., bleeding events, liver enzyme elevations and

clinical liver events, wound or joint complications), clinical laboratory tests (i.e., hematology, clinical chemistry, urinalysis), and physical examinations.

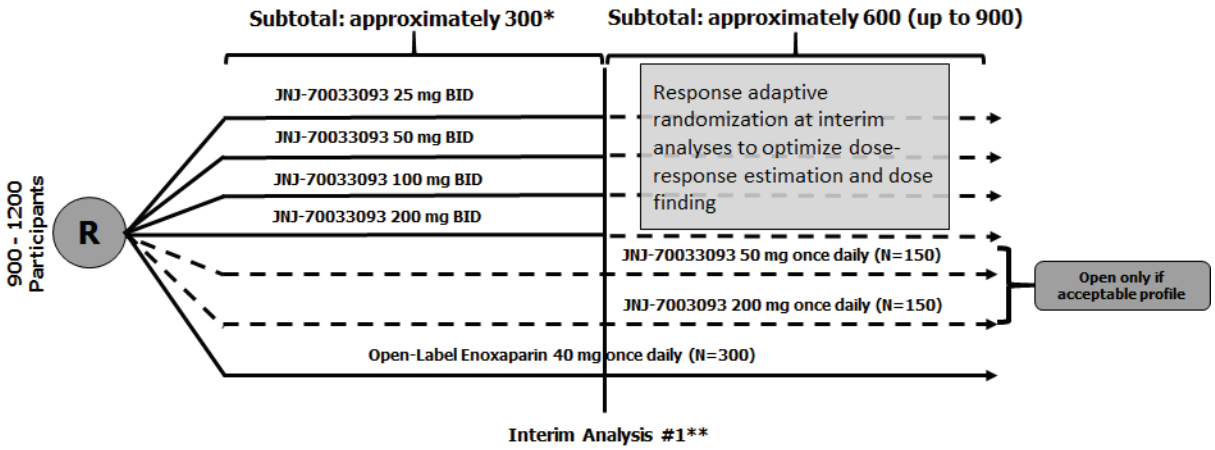
An Operations Committee (OC), Steering Committee, and independent Clinical Events Committee (CEC) will be commissioned for this study. The OC will be unblinded and the Steering Committee will be blinded to the dose and frequency of JNJ-70033093, unless the OC finds it necessary to consult with and unblind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

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

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

A diagram of the study design is provided in Figure 1.

**Figure 1: Schematic Overview of the Study**




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

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

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

## 1.3. Statistical Hypotheses for Trial Objectives

The study objectives include proof-of-efficacy and estimation of dose-response relationship in total VTE. This objective can be achieved either by showing a statistically significant dose-response trend (i.e., the alternative hypothesis is that there exists monotone dose-response trend), or by showing a statistically lower total VTE event rate in combined BID data compared with 30% (i.e., the alternative hypothesis is that the event rate of combined BID dose is less than 30%). The rate of 30% is a conservative estimate of the total VTE rate in subjects given placebo. The trend test consists of contrast tests defined by prespecified candidate models (4 $E_{max}$ dose-response modules with varying degrees of $ED_{50}$, Figure 2), which provide estimates of dose-response (taking BID and once daily into consideration).

## 1.4. Sample Size Justification

A target of 900 subjects will be randomly assigned to treatment in this study, with an option to increase the randomization target to approximately 1,200 subjects based on interim analysis results and/or evaluability rate.

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

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

**Table 1: Assumed Total VTE Event Rates by Treatment Group in Sample Size Determination**

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

BID = twice daily, VTE = venous thromboembolism

## 1.5. Randomization and Blinding

***Randomization***

Initially, subjects will be assigned in a 1:1:1:1:2 ratio into 1 of 5 treatment groups, including 4 dose regimens of JNJ-70033093 and enoxaparin 40 mg once daily based on an algorithm implemented in the interactive web response system (IWRS). Following the decision of altering randomization scheme by dropping and/or adding treatment arms, and/or changing randomization ratio, the IWRS will be updated for randomization accordingly. Subjects will be stratified by region using dynamic central randomization to minimize the imbalance in the distribution of the number of subjects across study drug groups. Based on the algorithm, the IWRS will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject.

***Blinding***

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the dosing blind for an individual subject. More details of blinding in the subject level could be found in Section 6.3 of the protocol amendment 1.

# 2. GENERAL ANALYSIS DEFINITIONS

## 2.1. Visit Windows

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. If a subject has 2 or more actual visits in one scheduled visit, the earliest visit will be used as the protocol visit for that analysis visit. This is mainly for the lab test analyses for the changes from baseline.

## 2.2. Pooling Algorithm

Not applicable.

## 2.3. Analysis Sets

Each analysis involves the following two aspects:

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

The following analysis sets: All Randomized Analysis Set, Intent-to-treat Analysis set (ITT), Safety Analysis Set, modified Intent-To-Treat Analysis Set (mITT), Per Protocol (PP) Analysis Set, and PK/PD Analysis Sets, will be used.

Associated with the analysis sets, three Analysis periods are defined as follows.

- Day 14: this period is defined as from Day 1 to Day 17 (inclusive).
- Week 6: this period is defined as from Day 1 to the last contact date.
- On-treatment: this period is defined as from Day 1 to last dose date + 2 days.

Day 1 refers to date of the first dose of study drug administration or the surgery date if the subject didn't take any study drug (see Section 2.5); Day 14 period and On-treatment period refer to the treatment period in different scenarios; Week 6 period refers to the full study period.

### 2.3.1. All Randomized Analysis Set

The all randomized analysis set includes all subjects who were randomized in the study regardless of whether they took study drug.

### 2.3.2. Intent-to-treat Analysis Set

The Intent-to-treat (ITT) (as termed Full Analysis Set [FAS] in the International Conference on Harmonization [ICH] E9 guideline) analysis set includes all randomized subjects who have signed an informed consent form.

### 2.3.3. Efficacy Analysis Sets

#### 2.3.3.1. Primary Efficacy Analysis Set

The modified Intent-to-treat (mITT) analysis set includes all ITT subjects who received at least 1 dose of study drug with an evaluable venography assessment or a confirmed symptomatic VTE event or any death as adjudicated by CEC. This will be identified as mITT (CEC).

Evaluable venography assessment at Day 14 is defined as the venography assessment with an evaluable result of the leg between Day 8 and Day 17. Subjects with unevaluable venography result as deemed by the CEC will be excluded from the primary efficacy analysis set mITT (CEC).

Primary efficacy analysis is based on the mITT analysis set associated with Day 14 analysis period.

In addition, the following distinctions will be implemented in data summary outputs whenever needed.

- Modified intent-to-treat analysis set (mITT) (Investigator) will be associated with investigator reported results.
- Modified intent-to-treat analysis set (mITT) (Best available) will be associated with the best available results, where best available event is defined as follows:
    - If an event is CEC adjudicated, then best available event is the CEC adjudicated event.
    - Otherwise, if an event is not CEC adjudicated, then best available event is the investigator reported event.

The mITT (Best available) analysis set will only be applicable to the interim analyses and the planned periodic reviews. At the time of database lock at the end of the study, all CEC adjudication of events will be completed. Hence, after the database lock, the mITT (Best available) analysis set will be identical to the mITT (CEC) analysis set.

#### 2.3.3.2. Secondary Efficacy Analysis Sets

The mITT analysis set at Week 6 is defined as the mITT analysis set at Day 14 plus the subjects who had no evaluable venography results at Day 14 visit but had symptomatic events or had evaluable venography results after Day 14 visit. The efficacy analysis based on this analysis set is associated with the Week 6 analysis period.

Per Protocol (PP) analysis set includes all mITT subjects with no key protocol deviations. Key protocol deviations are defined as follows,

- Developed withdrawal criteria but not withdrawn
- Randomized but did not satisfy key criteria
- Received a disallowed concomitant treatment
- Received study drug which is different from the treatment group randomized by the IWRS or an incorrect dose of study drug
- Was randomized but did not receive study drug

Key criteria are specified in the major protocol deviation document (TV-FRM-04718).

### 2.3.4. Safety Analysis Set

The safety analysis set includes all ITT subjects who received at least 1 dose (partial or complete) of study drug.

### 2.3.5. Pharmacokinetics Analysis Set

The PK analysis set consists of subjects who have received at least 1 dose of JNJ-70033093 and have at least one valid blood sample drawn for PK analysis.

### 2.3.6. Pharmacodynamics Analysis Set

The PD analysis set is defined as subjects who have received at least 1 dose of study drug and at least one valid blood sample drawn for PD analysis.

## 2.4. Definition of Subgroups

The following subgroups (see Table 2) will be used to summarize the total VTE efficacy and any bleeding event data.

**Table 2: Definition of Subgroups**

| Subgroup | Variant<br>Definition |
|---|---|
| Region | • Western Europe (Belgium, Greece, Israel, Italy, Portugal, South Africa, Spain)<br>• Eastern Europe (Bulgaria, Hungary, Lithuania, Latvia, Poland, Russia, Turkey, Ukraine)<br>• APAC (Asia Pacific: Australia, Japan, Malaysia, Thailand)<br>• LATAM (Latin America: Argentina, Brazil, Mexico)<br>• NA (North America: Canada and USA) |
| Age Group | • 50 - <65 years<br>• 65 - <75 years<br>• ≥75 years |
| Sex | • Female<br>• Male |
| Race | • White<br>• Asian<br>• African American<br>• Others |
| BMI | • underweight <18.5 kg/$m^2$<br>• normal 18.5-<25 kg/$m^2$<br>• overweight 25-<30 kg/$m^2$<br>• obese ≥30 kg/$m^2$ |
| D-Dimer | • ≥ 2X ULN*<br>• < 2X ULN* |
| Renal function (Creatinine Clearance Level) | • 30-<50 ml/min<br>• 50-<80 ml/min<br>• ≥ 80 ml/min |
| Surgery duration | • < 2 hours<br>• ≥ 2 hours |
| Tourniquet use | • Yes<br>• No |
| Aspirin/nonsteroidal anti-inflammatory drugs at baseline | • Yes<br>• No |

*ULN = upper limit of normal

## 2.5. Study Day and Relative Day

Day 1 refers to the date of the first dose of study drug administration or the surgery date if the subject didn't take any study drug. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

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

- Visit date - date of Day 1 + 1, if visit date ≥ date of Day 1
- Visit date - date of Day 1, if visit date < date of Day 1.

There is no 'Day 0'.

The last contact date is defined as the maximum of the following dates,

- Dates of all study-related visits (including scheduled or unscheduled visits);
- Dates of all study-related procedures, findings and events, including, but not limited to AE, concomitant medications, disposition, clinical laboratories, and death.

## 2.6. Baseline and Endpoint

Baseline is defined as the last observation prior to the first dose of study drug or the surgery if no study drug is taken.

Endpoint is defined as the available postbaseline result within the analysis period. Unscheduled visit results are included in this definition.

## 2.7. Imputation Rules for Missing Date/Time

Partial (missing) first dose (postoperative) date will be imputed as follows:

- If the partial date is missing day only, it will be set to:
    - First day of the month of the partial date, if month/year of the partial date is different than the month/year of the surgery day;
    - The surgery day if the month/year of the partial date is the same as the month/year of the surgery day.
- If the partial date is missing both day and month, it will be set to:
    - January 1 of the year of the partial date, if the year of this date is after the year of the surgery day;
    - The surgery day, if the partial date is the same year of the surgery day.

Completely missing first dose (postoperative) dates will not be imputed for the safety population.

Partial last dose date will be imputed as follows:

- If the partial last dose date is missing day only, it will be set to the earliest of
    - the last day of the month of the partial last dose date;
    - the surgery day + 14 days;
    - the evaluable venography day.
- If the partial last dose date is missing both day and month, it will be set to the earliest of
    - December 31 of the year of the partial last dose date;

  - the surgery day + 14 days;
  - the evaluable venography day.
- Completely missing last dose dates will not be imputed for the safety population.

Partial AE onset dates will be imputed as follows:

- If the onset date of an AE is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the first dose date;
  - The first dose date, if the month/year of the onset of AE is the same as month/year of the first dose date and month/year of the AE resolution date is different;
  - The first dose date or the day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the first dose date and month/year of the AE resolution date are same;
- If the onset date of an AE is missing both day and month, it will be set to, but no later than the AE resolution date:
  - January 1 of the year of onset date, as long as this date is on or after the first dose date;
  - Month and day of the first dose date, if this date is the same year that the AE occurred;
  - Last day of the year if the year of the AE onset is prior to the year of the first dose date;
- Completely missing onset dates will not be imputed.

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

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

Missing times of AE onset/resolution dates will be imputed as follows:

- A missing time of onset of an AE will be set to the earlier of:
  - 00:01 as long as the date is after Day 1;
  - The time of the first dose or the time of surgery for untreated subjects if this is the same day of Day 1.

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

# 3. PERIODIC AND INTERIM ANALYSES

The OC will be responsible for reviewing ongoing safety and efficacy data by unblinded subject treatment assignments approximately 3 to 8 weeks on a periodic basis. The first interim analysis will be triggered when approximately 300 subjects (approximately 50 subjects in each of the JNJ-70033093 BID treatment groups) will have completed the venography or have had a symptomatic VTE event. Additional interim analyses will be conducted, as needed, at the discretion of the OC.

Both periodic reviews and interim analyses will require an independent Statistical Support Group (SSG). Details of the operation of the OC are provided in the OC Charter. There will be no separate OC SAP.

## 3.1. Interim Analyses

The unblinded interim analyses will be conducted by the OC as part of the adaptive approach that may be used to guide decisions to drop a dose of JNJ-70033093, and/or adjust the randomization ratio based on available efficacy and safety data. The objectives of the interim analyses are to:

- Test futility
- Test dose-response trends to determine if the dose range being studied is appropriate for both efficacy and safety. Note, it is not intended that the study will stop early due to statistically significant dose-response trend
- Determine if a dose should be added and/or dropped to optimize data collection for dose-response modeling
- Determine how to allocate the remaining subjects optimally based on observed efficacy, safety or balanced efficacy/safety results.

Subjects randomization will be balanced in the active dose groups until the first OC committee review. Regarding adaptation guidelines, including futility, adding/dropping a dose, modification of the randomization ratio, see Section 7 of the OC Charter.

The first interim analysis will be triggered when approximately 300 subjects (approximately 50 subjects in each of the JNJ-70033093 BID treatment groups) will have completed the venography or have had a symptomatic VTE event. Before the first interim analysis OC meeting, a data cut-off date will be identified, and data cleaning efforts will be intensified in preparation for the creation of analysis data sets. The study programming team will transfer the blinded data to the SSG, and the IWRS vendor (Bracket) will transfer the randomization code to Secure Data Supplier (SDS). The SSG will then obtain the treatment assignment dataset from the SDS prior to the interim analysis and the unblinded report will be provided to the OC.

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

The significance level will not be adjusted for the final analysis.

# 4. SUBJECT INFORMATION

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

## 4.1. Demographics and Baseline Characteristics

Table 3 presents a list of the demographic variables and baseline characteristics that will be summarized for the ITT, mITT, PP and safety analysis sets.

**Table 3: Demographic Variables and Baseline Characteristics**

| **Continuous Variables:** | **Summary Type** |
|---|---|
| Age (years) | Descriptive statistics (total number [N], mean, standard deviation [SD]). |
| Weight (kg) | |
| Height (cm) | |
| Body Mass Index (BMI) (kg/m2) | |
| **Categorical Variables** | |
| Age (50 - <65 years, 65 - <75 years and ≥ 75 years) | Frequency distribution with the number and percentage of subjects in each category. |
| Sex (male, female) | |
| Race[a] (White, Asian, African American and others) | |
| Ethnicity (Hispanic or Latino, not Hispanic or Latino) | |
| BMI (underweight <18.5 kg/m2, normal 18.5-<25 kg/m2, overweight 25-<30 kg/m2, obese ≥30 kg/m2) | |
| Renal function (CrCl[b] 30-<50 ml/min, 50-<80 ml/min, ≥ 80 ml/min) | |
| D-Dimer (≥ 2X ULN[c], < 2X ULN) | |
| Surgery duration (< 2 hours, ≥ 2 hours) | |
| Tourniquet use (Yes, No) | |
| Aspirin/nonsteroidal anti-inflammatory drugs at baseline (Yes, No) | |
| Reason for surgery (Osteoarthritis, Rheumatoid arthritis, Osteonecrosis and Other) | |

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'
[b] CrCl = creatinine clearance. [c]ULN = upper limit of normal

## 4.2. Disposition Information

Screened subjects and reason for screen failures will be summarized.

The number of subjects in the following disposition categories will be summarized throughout the study:

- Subjects randomized
- Subjects randomized signing informed consent forms

- Subjects received study drug
- Subjects completed the study
- Subjects who prematurely discontinued study drug
- Subjects who completed study drug
- Reasons for discontinuation of study drug
- Subjects who terminated study prematurely
- Reasons for termination of study

Listings of subjects will be provided for the following categories:

- Subjects who prematurely discontinued study drug
- Subjects who terminated study prematurely
- Subjects who were unblinded to the dose level during the study period
- Subjects who were randomized yet did not receive study drug.

## 4.3. Treatment Compliance

Study drug compliance rate (%) will be calculated as: 100 * the actual number of days of study drug taken / the supposed number of days of study drug taken. More specifically, the actual number of days of study drug taken will be calculated as the minimum of [Day 10 date, last dose date, and the first primary efficacy outcome date] – first dose date + 1 – dose interruption days up to day 10. The supposed number of days of study drug taken will be calculated as the minimum of [day 10 date, and the first primary efficacy outcome date] - first dose date + 1.

Study drug compliance will be summarized descriptively.

## 4.4. Extent of Exposure

The number and percentage of subjects who receive study drug will be summarized. Descriptive statistics (N, mean, SD) for study drug duration will be presented for the safety analysis set.

## 4.5. Protocol Deviations

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

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

- Others

## 4.6. Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before Day 1. Concomitant medications are defined as any therapy used with a period overlapping with the period between the first dose and last dose of study drug, including those that started before and continued after the first dose of study drug.

Summaries of concomitant medications will be presented by anatomic and therapeutic class (ATC) term. The proportion of subjects who receive each concomitant medication will be summarized as well as the proportion of subjects who receive at least 1 concomitant medication. In addition, concomitant medications of special interest will be presented (see Attachment 1).

Prior medications will be summarized by ATC term.

# 5. EFFICACY

## 5.1. Analysis Specifications

### 5.1.1. Level of Significance

The primary hypothesis is that JNJ-70033093 reduces the risk of total VTE during the treatment period. This can be achieved by showing either a statistically significant dose-response trend (1-sided 5% significance level) or an event rate for the combined BID groups of JNJ-70033093 that is statistically lower than 30% (1-sided 5% significance level). The family wise error rate will be controlled at 1-sided 10%.

### 5.1.2. Data Handling Rules

Unless otherwise stated, all efficacy analyses and summaries will be performed using the treatment groups assigned by IWRS.

## 5.2. Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the total VTE, which is a composite of the proximal DVT (asymptomatic or symptomatic), distal DVT (asymptomatic or symptomatic), non-fatal PE and death.

### 5.2.1. Analysis Methods

The primary hypothesis, as defined in Section 5.1.1., will be tested with its two components, respectively. The first component, the total VTE event rate lower than 30% in the combined BID doses of JNJ-70033093 in the mITT analysis set and Day 14 analysis period, will be tested at a 1-sided 5% significance level. In other words, the following hypothesis will be tested:

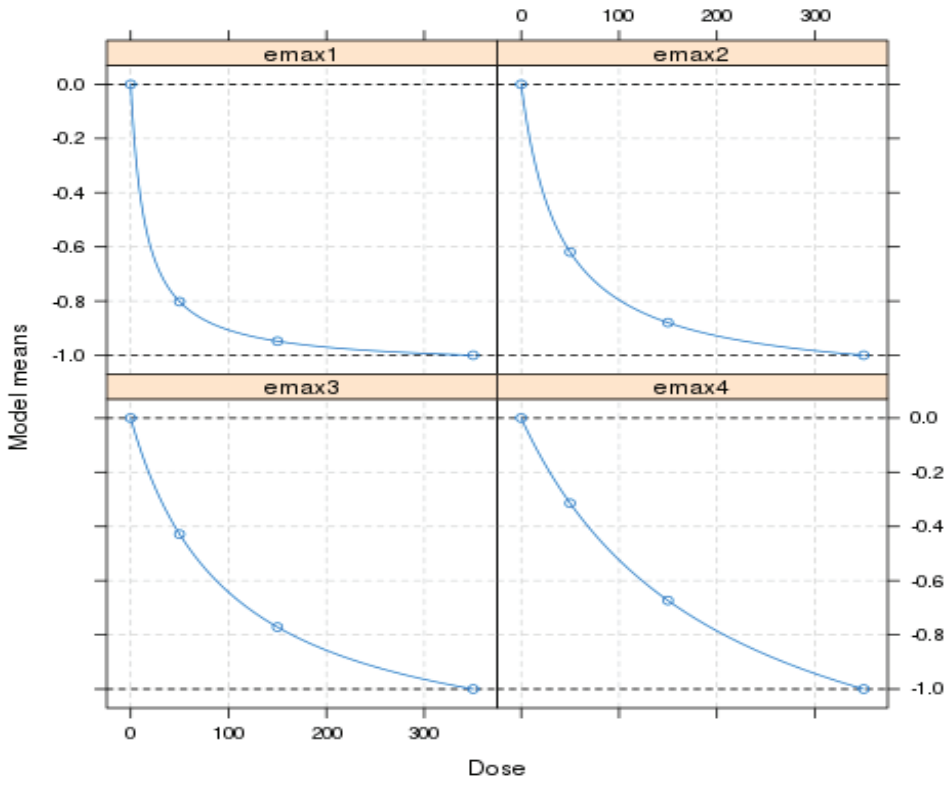
$H_0: Total\ VTE\ Rate \geq 0.3$ Versus $H_1: Total\ VTE\ Rate < 0.3$

Binomial test will be employed to test the hypothesis.

The second component, the dose-response trend test based on the MCP-Mod[1] framework, will consist of contrast tests defined by prespecified candidate models (4 $E_{max}$ dose-response models with varying degrees of $ED_{50}$, Figure 2), which provide estimates of dose-response (taking BID and once daily into consideration).

The MCP-Mod framework determines a set of optimal model contrasts. Each model will then be evaluated for significance of trend, based on its optimal contrast, resulting in four t-test statistics, one for each candidate model. The t-test statistics will have been adjusted for the fact that multiple candidate models (four) have been included in the trend testing. The efficacy of the drug is then established if the maximum of the t-test statistics exceeds the 95$^{th}$ percentile critical value (one-sided significance level 5%).

**Figure 2: Canonical Candidate $E_{max}$ Dose-response Models Used in the MCP-Mod Analysis**




## 5.3. Major Secondary Efficacy Endpoints

Major secondary efficacy endpoints include all individual components of the primary efficacy endpoint

- Proximal DVT
  - Asymptomatic
  - Symptomatic
- Distal DVT

  - Asymptomatic
  - Symptomatic
- Nonfatal PE
- Any death
- Major VTE
  - Proximal DVT
  - Nonfatal PE
  - Any death

### 5.3.1. Analysis Methods

For the major secondary efficacy endpoints, event rate (incidence) of the total VTE and the individual components in the Day 14 period and the Week 6 period will be summarized by treatment group for the mITT analysis set. The 95% confidence intervals for the relative risk ratio (RR) of each JNJ-70033093 dose group compared with enoxaparin group will also be constructed. The relative risk ratios (RR) and their corresponding confidence intervals will be calculated using Cochran-Mantel-Haenszel method[2,3] with region as a stratification factor.

Additional sensitivity analyses may be explored in ITT, PP, safety population, and/or a subset of the ITT population consisting of subjects with a valid assessment of potential efficacy outcome within Day 14 and/or Week 6 analysis periods.

## 5.4. Exploratory Efficacy Variable(s)

### 5.4.1. Definition

The exploratory efficacy variables are defined as

- To evaluate PD to assess its relationships to PK and the relation of these measures to efficacy and safety endpoints (e.g., exposure-response analyses);
- To evaluate exploratory biomarkers to assess their relationship to the probability of total VTE during the treatment period;
- To explore the presence and incidence of asymptomatic MINS as it relates to total knee arthroplasty.

### 5.4.2. Analysis Methods

The analysis method for the exploratory efficacy variables will be detailed in separate PK and/or PD analysis documents.

# 6. SAFETY

All safety analyses will be based on the safety analysis set of actual treatment received, unless otherwise specified.

For all continuous safety variables, descriptive statistics will include N, mean and SD. Categorical variables will be summarized using frequency counts and percentages.

## 6.1. Principal Safety (Bleeding) Endpoint

The principal safety endpoint is any bleeding event, as adjudicated by CEC, which is defined as the composite of major bleeding, clinically relevant non-major (CRNM) bleeding, and minimal bleeding events. Major bleeding refers to the ISTH major bleeding in the surgical setting.

### 6.1.1. Principal Safety (Bleeding) Analysis Methods

The analysis for safety (bleeding) events has two parts. The first part will focus on the event rate (incidence) within specified study period, which will be implemented by comparing the event rate of each study drug group with the event rate in the enoxaparin group. The analysis method will be the same as the method for major secondary efficacy analysis. Please refer to Section 5.3.1 for details.

The second part of the analysis will be the analysis of time-to-event data. Specifically, analyses based on Kaplan-Meier (K-M) estimates[4] of time from day 1 to the first occurrence of any bleeding event (composite of major, CRNM and minimal bleeding events) will be implemented for each JNJ-70033093 dose group and enoxaparin over the on-treatment period and the Week 6 period.

For the time-to-event analyses, subjects who do not experience any bleeding event during the on-treatment period will be censored at the earliest of the last dose date + 2 days, death date or the last contact date. Similarly, subjects who do not experience any bleeding event during the Week 6 period will be censored at week 6 + 10 days, death date or the last contact date, whichever occurs first.

Frequency distribution of per subject total number of bleeding events will be summarized by dose group using the counts 0, 1, 2 and $\geqslant$ 3.

Sensitivity analyses of bleeding reported by the investigator and/or by comparing the CEC adjudicated event rates in the postoperative period may be presented. Concordance of events between CEC and investigator reported may also be assessed.

Estimation of dose-response relationship in any bleeding will also be assessed by MCP-Mod approach.

## 6.2. Major Secondary Safety (Bleeding) Endpoints

Major secondary safety (bleeding) endpoints include the following components of the principal safety endpoint,

- Major bleeding,
- Clinically relevant non-major bleeding,
- Clinically relevant bleeding, including both major and non-major,

- Minimal bleeding

### 6.2.1. Major Secondary Safety (Bleeding) Endpoints Analysis Methods

The statistical analysis method for the major secondary safety (bleeding) endpoints will be similar to the analysis method for the principal safety endpoint. See Section 6.1.1. for details.

## 6.3. Adverse Event

The verbatim terms used in the eCRF by investigators to identify an AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study drug through the day of last dose plus 2 days is considered as treatment emergent. If the event occurs on the day of the initial administration of study drug, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered as treatment emergent unless it is known to be prior to the first administration of study drug based on the partial date. All reported treatment emergent adverse events (TEAE) will be included in the analysis. For each AE, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summary tables will be provided for:

- All AEs, TEAEs, AEs occurred 2 days after the last dose date, and AEs after the first dose date.
- All SAEs, treatment emergent serious adverse events (TESAEs), and SAEs occurred 2 days after the last dose date, and SAEs after the first dose date.
- AEs leading to discontinuation of study drug
- TEAEs by severity

Incidence of other TEAEs of interest will be summarized.

As per protocol, AEs of interest include bleeding events, wound or joint complications, liver enzyme elevations and clinical liver events. All suspected thrombotic events will also be captured as AEs of interest. Subjects with AEs of interest may be counted or listed using MedDRA SMQs (e.g., hemorrhage excluding laboratory terms SMQ).

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

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

## 6.4. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the subjects included in the safety analysis set.

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

Changes from baseline to scheduled time points will be summarized for chemistry, hematology and specific components of urinalysis tests and displayed by treatment group.

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

Clinically important abnormal laboratory findings to be reported are described below:

- ALT and/or AST (U/L): ≥ 3x ULN.
- Markedly abnormal laboratory findings to be reported are described below:
- ALT and/or AST (U/L) ≥5x ULN
- ALT and/or AST (U/L) ≥ 10x ULN
- Hemoglobin < 80g/L
- Platelet < 50,000/uL

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

## 6.5. Vital Signs

Vital signs measurements are not being collected in this study.

# 7. PHARMACOKINETICS/PHARMACODYNAMICS

## 7.1. Pharmacokinetics

PK analyses will be performed on the PK analysis set, defined as subjects who have received at least 1 dose of JNJ-70033093 and have at least 1 valid blood sample drawn for PK analysis.

Descriptive statistics (N, mean, SD, median, range, Coefficient of Variation [CV %] and IQ range) will be used to summarize JNJ-70033093 plasma concentrations at each nominal sampling time point by treatment.

JNJ-70033093 plasma concentrations below the lower limit of quantitation will not be imputed and will be noted in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented.

Population PK analysis using plasma concentration-time data of JNJ-70033093 will be performed using nonlinear mixed-effects modeling. Details will be given in a separate population PK analysis plan and the results of the analysis (including the exposure-response analyses) will be presented in a separate report.

## 7.2. Pharmacodynamics

PD analyses will be performed on the PD analysis set, defined as subjects who have at least one valid blood sample drawn for PD.

Descriptive statistics (N, mean, SD, median, range, CV (%) and IQ range) will be used to summarize PD response at each nominal sampling time point by treatment group. Changes from baseline will be summarized when applicable.

PD response outside of limit of quantitation will not be imputed and will be noted in the summary statistics.

## 7.3. Pharmacokinetic/Pharmacodynamic Relationships

Relationships between PD (including aPTT, PT, FXI clotting activity, anti-FXa activity, and TGA) and PK will be evaluated. The relationship between PK and efficacy, as well as between PK and safety endpoints (e.g., exposure-response analyses) will also be evaluated. These analyses will be outlined in a separate population PK analysis plan and reported in a separate population PK report.

# 8. BIOMARKERS

Descriptive statistics (N, mean, SD, median, range, CV (%) and IQ range) will be used to summarize exploratory biomarker response (including D dimer, high-sensitive cardiac troponin T [hs-cTnT], and FXI antigen) at each nominal sampling time point by treatment group. Changes from baseline will be summarized when applicable.

## REFERENCES

1. Pinheiro JC, Bornkamp B, Glimm E, Bretz F. 2014. “Model-based dose findings under model uncertainty using general parametric models.” *Statistics in Medicine*. 33:1646-1661.
2. Cochran, William G. 1954. “Some Methods for Strengthening the Common Chi-Squared Tests.” *Biometrics* 10 (4). [Wiley, International Biometric Society]: 417–51.
3. Mantel, N., and W. Haenszel. 1959. “Statistical Aspects of the Analysis of Data from Retrospective Studies of Disease.” *Journal of the National Cancer Institute* 22 (4): 719–48.
4. Kaplan, E. L., and Paul Meier. “Nonparametric Estimation from Incomplete Observations.” *Journal of the American Statistical Association* 53, no. 282 (1958): 457–81.

# ATTACHMENTS

### Attachment 1: Medications of Special Interest

Concomitant medications of special interest are defined as follows:

| **Concomitant Medication Special Interest Category** | **Standard ATC Group Name** | ATC Group Code | **Standard Medication Name** | ATC code |
|---|---|---|---|---|
| ANTITHROMBOTIC AGENTS | Heparin group | B01AB | heparin | B01AB01 |
| | | | antithrombin III | B01AB02 |
| | | | dalteparin | B01AB04 |
| | | | enoxaparin | B01AB05 |
| | | | nadroparin | B01AB06 |
| | | | parnaparin | B01AB07 |
| | | | reviparin | B01AB08 |
| | | | danaparoid | B01AB09 |
| | | | tinzaparin | B01AB10 |
| | | | sulodexide | B01AB11 |
| | | | bemiparin | B01AB12 |
| | | | | |
| | Platelet aggregation inhibitors excl. heparin | B01AC | clopidogrel | B01AC04 |
| | | | ticlopidine | B01AC05 |
| | | | acetylsalicylic acid | B01AC06 |
| | | | dipyridamole | B01AC07 |
| | | | carbasalate calcium | B01AC08 |
| | | | iloprost | B01AC11 |
| | | | abciximab | B01AC13 |
| | | | eptifibatide | B01AC16 |
| | | | tirofiban | B01AC17 |
| | | | treprostinil | B01AC21 |
| | | | prasugrel | B01AC22 |
| | | | cilostazol | B01AC23 |
| | | | ticagrelor | B01AC24 |
| | | | cangrelor | B01AC25 |
| | | | | |
| | Enzymes | B01AD | streptokinase | B01AD01 |
| | | | alteplase | B01AD02 |
| | | | anistreplase | B01AD03 |
| | | | urokinase | B01AD04 |
| | | | reteplase | B01AD07 |
| | | | drotrecogin alfa (activated) | B01AD10 |
| | | | tenecteplase | B01AD10 |
| | | | | |
| | Direct thrombin inhibitors | B01AE | desirudin | B01AE01 |
| | | | lepirudin | B01AE02 |
| | | | argatroban | B01AE03 |
| | | | melagatran | B01AE04 |

| **Concomitant Medication Special Interest Category** | **Standard ATC Group Name** | ATC Group Code | **Standard Medication Name** | ATC code |
|---|---|---|---|---|
| | | | ximelagatran | B01AE05 |
| | | | bivalirudin | B01AE06 |
| | | | dabigatran etexilate | B01AE07 |
| | | | | |
| | Direct factor Xa inhibitors | B01AF | rivaroxaban | B01AF01 |
| | | | apixaban | B01AF02 |
| | | | edoxaban | B01AF03 |
| | Other antithrombotic agents | B01AX | defibrotide | B01AX01 |
| | | | fondaparinux | B01AX05 |
| | | | | |
| VITAMIN K AND OTHER HEMOSTATICS | Local hemostatics | B02BC | thrombin | B02BC06 |
| | | | | |
| ANTIFIBRINOLYTICS | Amino acids | B02AA | tranexamic acid | B02AA02 |
| | | | aminocaproic acid | B02AA01 |
| NASAL DECONGESTANTS FOR SYSTEMIC USE | Sympathomimetics | R01BA | phenylpropanolamine | R01BA01 |
| | | | pseudoephedrine | R01BA02 |
| | | | phenylephrine | R01BA03 |
| | | | phenylpropanolamine, combinations | R01BA51 |
| | | | pseudoephedrine, combinations | R01BA52 |
| | | | | |
| OTHER ANALGESICS AND ANTIPYRETICS | Salicylic acid and derivatives | N02BA | carbasalate calcium | N02BA15 |
| | | | carbasalate calcium combinations excl. psycholeptics | N02BA65 |
| INTESTINAL ANTIINFLAMMATORY AGENTS | Aminosalicylic acid and similar agents | A07EC | sulfasalazine | A07EC01 |
| | | | | |
| ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS | ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS | M01A | Butylpyrazolidines | M01AA |
| | | | Acetic acid derivatives and related substances | M01AB |
| | | | Oxicams | M01AC |
| | | | Propionic acid derivatives | M01AE |

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