Official Title of Study:

A Phase IV, Open-Label, Multi-center Study to Evaluate the Safety of Apixaban in Indian Subjects Undergoing Elective Total Knee Replacement or Total Hip Replacement Surgery

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STATISTICAL ANALYSIS PLAN FOR CLINICAL STUDY REPORT

A Phase IV, Open-Label, Multi-center Study to Evaluate the Safety of Apixaban in Indian Subjects Undergoing Elective Total Knee Replacement or Total Hip Replacement Surgery

PROTOCOL CV185158

V2.0

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DOCUMENT HISTORY

Version Number	Author(s)	Description
1.0	[redacted]	Original Version
2.0	[redacted]	1.Efficacy is not primary endpoint. There is no sensitivity analysis on evaluable population needed. Thus the definition of evaluable population and corresponding planned analyses were deleted now. 2. Original treatment compliance formula is not accurate. It's adjusted to current version.

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1.1 Research Hypothesis

Apixaban 2.5 mg twice a day in Indian patients undergoing hip or knee replacement surgery will provide an acceptable rate of ISTH major/CRNM bleeding.

1.2 Schedule of Analyses

A final analysis will be performed after all subjects either complete the 2 weeks (for knee replacement subjects) or 5 weeks (for hip replacement subjects) treatment period followed by a 30-day follow-up period, or discontinue prematurely. There is no interim analysis planned for this study.

2 STUDY DESCRIPTION

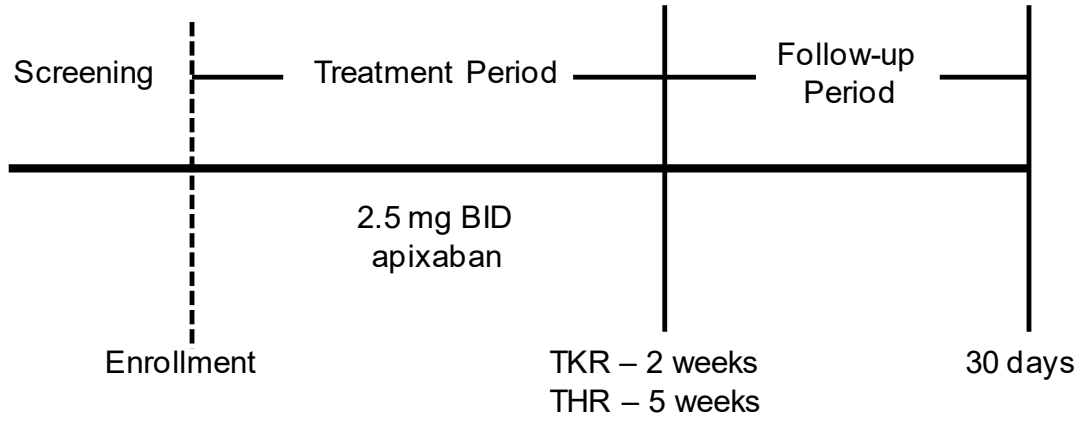
2.1 Study Design

Expected duration of the study, from first subject, first visit through last subject, last visit is approximately 8 months.

This study is designed to evaluate the safety of oral apixaban 2.5 mg BID following total knee and hip replacement surgeries. There are four study periods extending up to maximum duration of approximately 42 ± 2 days for the patients undergoing total knee replacement surgery and up to 65 ± 2 days for the patients undergoing total hip replacement surgery:

- A screening period, of up to 14 days prior to surgery
- An enrollment period: from 4 days before surgery to 1 day after surgery
- A treatment period: First dose, PO, starting 12 - 24 hours after completing skin wound closure, then BID for 35 ± 2 days for the subjects undergoing total hip replacement or 12 ± 2 days for the subjects undergoing total knee replacement.
- A 30-day follow-up period starting the day after the last dose of study medication.

Figure 2.1 Study Design



2.2 Treatment Group Assignment

Apixaban 2.5 mg bid.

2.3 Blinding and Unblinding

Not applicable.

3 OBJECTIVES

3.1 Primary Objective

To evaluate that oral administration of apixaban 2.5 mg twice a day for 2 weeks (for knee replacement subjects) or 5 weeks (for hip replacement subjects) is well tolerated in Indian subjects and produces an acceptable rate of ISTH major/CRNM bleeding.

3.2 Secondary Objectives

To evaluate that oral administration of apixaban 2.5 mg twice a day for 2 weeks (for knee replacement subjects) or 5 weeks (for hip replacement subjects) produces an acceptable rate of the composite of VTE/all cause death.

4 ENDPOINTS

4.1 Primary Endpoint

The primary study endpoint is a composite of International Society on Thrombosis and Haemostasis (ISTH) major bleeding/clinically relevant non-major bleeding (CRNM) in subjects undergoing elective total knee or hip replacement at the end of treatment + 2 days, where ISTH major bleeding is

- Fatal or
- Bleeding in a critical organ, such as brain, spine, eye, retroperitoneum, joint, heart sac, or skeletal muscle (and resulting in compartment syndrome), or

- Bleeding that results in a fall of hemoglobin of 2 g/dL or more or transfusion of 2 units or more of packed red cells or whole blood within 24 hours

and CRNM bleeding is bleeding that

- Is clinically acute and overt
- Does not satisfy criteria as a major bleed but requires medical intervention, such as a visit to a physician's office, emergency room, or urgent care center for epistaxis.

4.2 Secondary Endpoint

The secondary endpoint will be: The composite of VTE/all cause death at the end of treatment + 2 days, where VTE is the combination of deep vein thrombosis and non-fatal pulmonary embolism.

5 SAMPLE SIZE AND POWER

The sample size of the study is determined by requirement of regulatory agency rather than statistical considerations. With 500 subjects in the apixaban arm and event rate of 4.36% for ISTH major or clinically relevant non-major bleeding, the width of the 95% CI for the event rate will be (2.6%, 6.2%) and width of the CI is 3.6%.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

In all listings, summaries and statistical analyses, the term '**Intended Treatment Period**' refers to the period that starts with the enrollment.

In all listings, summaries and statistical analyses, the term '**Treatment Period**' will refer to the period between the first administration of study medication (post-surgery oral apixaban) and 2 days after the last administration of study medication (end of treatment). This period will be the basis for the summaries of safety and efficacy.

In all listings, summaries and statistical analyses, the term "**Follow-up Period**" will refer to the period starting after the "Treatment Period" ended through 30 days after discontinuation of study drug (for treated subjects).

6.2 Treatment Regimens

Safety and efficacy outcomes will be summarized according to the **Treated** group, which subjects who received at least one dose of study drug.

6.3 Populations for Analyses

The following populations will be used for the analyses:

Enrolled Population

The Enrolled Subjects population consists of all subjects who signed informed consent.

Treated Population

The treated population consists of all subjects who received at least one dose of study drug during the treatment period. In the treated population, subjects are categorized to the **As Treated** group.

Efficacy Population

Same as Treated Population.

7 STATISTICAL ANALYSES

Type of surgery (knee surgery or hip surgery) will be included as subgroup factor in some of the efficacy (Section 7.5) and all safety summaries (Section 7.6) as well as when summarizing demographic and baseline characteristics (Section 7.3) and extent of exposure (Section 7.4).

7.1 General Methods

Refer to Section 7.1 of the Core SAP for VTE Prevention for further details on statistical methods.

7.2 Study Conduct

Significant protocol deviations will be identified for all subjects who are treated.

7.3 Study Population

7.3.1 Subject Disposition

Refer to Section 7.3.1 of the Core SAP for VTE Prevention.

7.3.2 Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all subjects combined, using treatment data set. All summaries will be further tabulated by stratification factor of type of surgery (knee or hip). Continuous variables will be summarized using mean and standard deviation. Categorical variables will be summarized using relative frequency.

Key demographic and baseline variables to be summarized include: age, gender, race, vital signs (systolic blood pressure, diastolic blood, pressure, and heart rate), medical history, knee or hip replacement surgery experience, intra-operative details, and post-surgical patient care characteristics.

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7.4 Extent of Exposure

7.4.1 Study Therapy

Extent of exposure to the study drug is defined as the number of the days the subject is known on study drug. Summary to exposure to study drug will show the distribution of the number of days on drug, together with the mean days of exposure, by type of surgery (knee or hip).

Treatment compliance (TC) will also be summarized by type of surgery (knee or hip).

For each treated subject, treatment compliance with apixaban (BID) regimen is defined as follows:$TC = \frac{100*\text{number of tablets taken}}{number\ of\ days\ from\ first\ to\ last\ post-surgery\ open\ label\ dose*2-k}\%$

where

k=0, if the first dose is given the day after surgery

k=1, if the first dose is given on the day of surgery.

In addition, time from the end of surgery to first post-operative dose of study medication will be summarized by type of surgery (knee or hip).

7.4.2 Prior and Concomitant Medications

Refer to Section 7.4.2 of the Core SAP for VTE Prevention.

7.5 Efficacy

The event rates and their 95% confidence intervals of composite of venous thromboembolism (VTE) and all cause death based on efficacy population will be summarized. Subgroup summary by surgery type (knee or hip) will also be conducted.

7.6 Safety

Bleeding is the primary safety outcome measure. The event rate of adjudicated major bleeding or clinically relevant non-major bleeding events during the treatment period will be summarized. Subgroup summary for bleeding by surgery type (knee or hip) will also be conducted.

The incidence of adverse events will be summarized for both the treatment and follow-up period by surgery type (knee or hip). Any post-dose marked abnormalities in clinical laboratory tests will be listed.

All adverse events that are serious or that result in discontinuation of study therapy will be described in depth.

7.6.1 Adverse Events

Refer to Section 7.6.2.1 in the Core SAP for VTE Prevention.

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7.6.2 Laboratory Data

Refer to Section 7.6.2.2 in the Core SAP for VTE Prevention. Hemoglobin is the parameter which will be summarized.

7.6.3 Events of Special Interest

Refer to Section 7.6.2.4 in the Core SAP for VTE Prevention.

8 CONVENTIONS

8.1 Safety Data Conventions

Refer to Section 8.1 of the Core SAP for VTE Prevention.

8.2 Baseline Measurements

Refer to Section 8.2 of the Core SAP for VTE Prevention.

8.3 Day Ranges for Analysis of Time Points

Subjects do not always adhere strictly to the visit schedule timing in the protocol. The day ranges for the summary of laboratory measurements are defined in the following tables.

Table 8.3A: Day Ranges for summary of Laboratory Measurements

Nominal Visit	Target Day	Day Ranges
Screening	Pre-Surgery 1-14 day	Screening to < Enrollment
Enrollment	Pre-Surgery -4 day - 24 hours	Enrollment to < start of surgery
Hospital discharge	Hospital discharge	Day 2 to < End of treatment period

8.4 Multiple Measurements

Refer to Section 8.4 of the Core SAP for VTE Prevention.

9 CONTENT OF REPORTS

Refer to Section 9 of the Core SAP for VTE Prevention.

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APPENDIX 1 ANALYSIS OF SAFETY DATA - REFERENCE TO CT SOP 109

The original GD SOP 12 in Core SAP is retired and replaced by CT SOP 109.

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REFERENCES

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