Janssen Research & Development *

Statistical Analysis Plan

A Prospective, Open-Label, Active-Controlled Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Efficacy of Rivaroxaban for Thromboprophylaxis in Pediatric Subjects 2 to 8 Years of Age after the Fontan Procedure (UNIVERSE Study)

Protocol 39039039CHD3001; Phase 3

JNJ-39039039; BAY 59-7939 (rivaroxaban)

Amendment 1

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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

ASA	Acetyl Salicylic Acid
aPTT	Activated Partial Thromboplastin Time
AXA	Anti-FXa Activity
CI	Confidence Interval
CIAC	Central Independent Adjudication Committee
CrCl	Creatinine Clearance
DPS	Data Presentation Specifications
DRC	Data Review Committee
EC	Executive Committee
eCRF	Electronic Case Report Form
ESMD	Early Study Medication Discontinuation
IDMC	Independent Data Monitoring Committee
ISTH	International Society on Thrombosis and Haemostasis
IWRS	Interactive Web Response System
KM	Kaplan-Meier
PBPK	Physiologically-based Pharmacokinetic
PD	Pharmacodynamics
PT	Prothrombin Time
PK	Pharmacokinetics
SAP	Statistical Analysis Plan
SC	Sponsor Committee
TE	Treatment-Emergent
TEAE	Treatment-Emergent Adverse Events

SAP AMENDMENT

SAP Version	Issue Date
Original SAP	November 15th, 2016
Amendment 1	May 16th, 2019

The principal rational for the SAP Amendment 1 is to clarify the definition of the categories and terms of key protocol deviations considered for the Per protocol Set. Also, PK/PD analysis plan in Section 6 was updated to include Part B data, and Attachment 1 was removed because a full PK/PD data analysis plan will be provided separately.

1. INTRODUCTION

This Statistical Analysis Plan (SAP) specifies definitions of analysis sets, key derived variables, and statistical methods for analysis of safety and efficacy data, as well as statistical summaries of PK and PD findings for the Phase 3 study 39039039CHD3001 (also known as UNIVERSE). This SAP is based on the Protocol 39039039CHD3001, Amendments INT-1 and INT-2, which were finalized on April 7th, 2016 and July 28th, 2017, respectively. Titles, mock-ups and programming instructions for all statistical outputs (tables, figures, and listings) are provided in a separate document entitled Data Presentation Specifications (DPS).

1.1 Trial Objectives

The primary objective of Part A of the study is to characterize the single- and multiple-dose pharmacokinetics (PK) and pharmacodynamics (PD) profiles after oral rivaroxaban therapy administered to pediatric subjects 2 to 8 years of age with single ventricle physiology who have completed the Fontan surgery within 4 months prior to enrollment. The secondary objective of Part A is to assess the safety and tolerability of rivaroxaban treatment.

The primary objective of Part B is to evaluate the safety and efficacy of rivaroxaban, administered twice daily (total daily exposure matched to rivaroxaban 10 mg once daily in adults) compared to acetylsalicylic acid (ASA), given once daily (approximately 5 mg/kg) for thromboprophylaxis in pediatric subjects 2 to 8 years of age with single ventricle physiology who have completed the Fontan surgery within 4 months prior to enrollment. The secondary objective in Part B is to further characterize the PK and PD profiles of rivaroxaban.

1.2 Trial Design

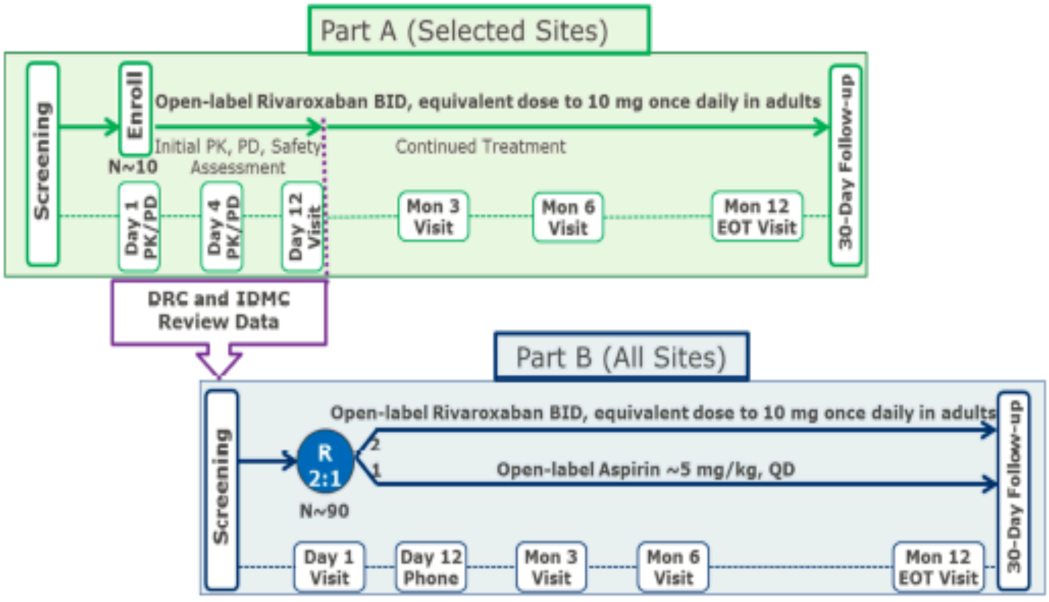
This is a prospective, open-label, active-controlled, multicenter study designed to evaluate the PK and PD profiles, safety and efficacy of rivaroxaban for thromboprophylaxis in pediatric subjects 2 to 8 years of age with single ventricle physiology who have completed the Fontan surgery within 4 months prior to enrollment.

The two parts of the study are as follows:

- Part A: This is the 12-month, non-randomized, open-label, part of the study which includes an Initial PK, PD and Safety Assessment Period. The Data Review Committee (DRC) will assess by Day 12 the single- and multiple-dose rivaroxaban PK, PD and the initial safety and tolerability data available from each subject, prior to the subject continuing in the study to complete the planned 12 months of open-label rivaroxaban therapy of Part A. Subjects in Part A will not participate in Part B.
- Part B: This is the randomized, open-label, active-controlled part of the study that will evaluate the safety and efficacy of rivaroxaban compared to ASA for thromboprophylaxis for 12 months. Subjects randomized to rivaroxaban will also have PK and PD assessments.

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

Figure 1: Schematic Overview of Study 39039039CHD3001



Note: An internal DRC will assess before the Day 12 Visit, the PK, PD, and safety data from each subject, prior to the subject continuing in the study to complete the planned 12 months of open-label rivaroxaban therapy. Enrollment in Part A will end, and enrollment in Part B will start, once the cumulative data from all subjects in the Initial PK, PD, and Safety Assessment Period of Part A are deemed acceptable by the IDMC.

1.3 Statistical Hypotheses for Trial Objectives

There is no formal hypothesis testing for this study.

1.4 Sample Size Justification

A total of at least 100 pediatric subjects overall are planned to be enrolled in this study. Due to the limited availability of the study population and the expected low event rates, this study is not powered to test formal hypothesis for efficacy. The total sample size is based on regulatory feedback to obtain sufficient safety data in this pediatric population.

The sample size of approximately 10 subjects for Part A is considered adequate for the initial PK assessment of rivaroxaban in the studied pediatric subjects. Approximately 90 subjects will be enrolled into Part B of the study.

1.5 Randomization and Blinding

Subjects in Part A will not be randomized.

Randomization in Part B of this study will begin once the cumulative subjects' data from initial PK and Safety Assessment in Part A are deemed acceptable by the IDMC.

Central randomization will be implemented in this study for Part B: approximately 90 subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor; the assignment to treatment groups will be 2 to 1 (rivaroxaban to ASA).

The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment for the subject. The requestor of the treatment code/randomization must use his or her own user identification and personal identification number when contacting the IWRS to receive the relevant subject details to uniquely identify the subject. The study drug number will be assigned and recorded in the IWRS.

As this is an open-label study, blinding procedures are not applicable. Open-label treatment will be used to allow for further evaluation of the PK and PD profiles of rivaroxaban throughout the study.

1.6 Interim Analysis and Committees

No interim analysis is planned to be conducted in this study (PK evaluation in Part A is not considered interim analysis.)

1.6.1 Data Review Committee (DRC)

The DRC consists of members from the sponsor not directly involved in the conduct of the study, who will evaluate the PK and safety of each subject in Part A, and who will evaluate that information relative to the physiologically-based pharmacokinetic (PBPK) model predictions. The DRC will assess the PK, PD, and the safety data available from each subject, prior to the subject continuing in the study to complete the planned 12 months of open-label rivaroxaban therapy. The DRC will only operate during the initial PK, PD, and safety assessment period of Part A.

The DRC review package for individual subjects may include the following 3 parts (details are provided in a separate DRC Charter document that details the process of DRC review):

- PK data: rivaroxaban AUC_{0-24}, C_{max} and C_{min} on Days 1 and 4.
- PD data: PT and aPTT values at baseline and Days 1 and 4; time-matched PT and aPTT versus rivaroxaban plasma concentration plots on Days 1 and 4.
- Safety data: all available subject information including but not limited to demographic information, medical history, baseline lab values, dosing information, adverse events and outcome events (including best available bleeding and thrombotic events).

1.6.2 Independent Data Monitoring Committee (IDMC)

The IDMC will evaluate PK, PD, safety and efficacy data to ensure subject safety throughout the study. The IDMC will be an independent expert advisory group external to the sponsor and study. For Part A only, the IDMC will review the cumulative data from the Initial PK, PD, and Safety Assessment Period and will provide the recommendation to the EC and sponsor committee to cease enrollment in Part A and to start enrollment directly into Part B. The IDMC will operate for both Part A and Part B. The acceptability criteria will be described in the IDMC charter.

1.6.3 Central Independent Adjudication Committee (CIAC)

The CIAC is comprised of specialist physicians as appropriate and necessary. Committee members do not directly enroll subjects in the study, are not involved in the study monitoring, and do not have direct operational responsibilities for the conduct of the study. Members will review all safety and efficacy outcomes that occur post- enrollment as they become available and

adjudicate and classify the following events in a consistent and unbiased manner according to definitions in the CIAC charter while blinded to treatment assignment:

Safety and efficacy outcomes include bleeding events, any thrombotic event (venous or arterial), other vascular events, and deaths that occur during the study and the 30-day post-study treatment period.

Sites will be required to complete a worksheet, compile an adjudication package, and to send it to the adjudication office within 6 weeks from occurrence of the event. The CIAC procedures will be described in the CIAC charter. Adjudication results will be the basis for the final analyses.

The best available data will be used for DRC and IDMC reviews. The CIAC-adjudicated results will be used in the final analysis for all subjects.

1.6.4 Executive Committee (EC)

The EC will provide overall academic leadership for the study and will oversee the conduct and the publications of the results. In addition, the EC will receive recommendations from the IDMC regarding modification to the study and will decide whether to accept the recommendations. The EC will have 2 co-chairs and will consist of members of academic institutions and 1 member from the sponsor.

2. GENERAL ANALYSIS DEFINITIONS

Statistical analysis of the overall study data will be done by the sponsor.

Description of the statistical methods to be used to analyze the efficacy and safety data is outlined in this document, including imputation rules for missing or partially missing dates.

Summaries by treatment group using appropriate descriptive statistics will be provided for study variables. Descriptive statistics such as mean, median, standard deviation, 95% CIs (when applicable), minimum, and maximum will be used to summarize continuous variables; Counts and percentages will be used to summarize categorical variables. The Kaplan-Meier (KM) method will be used to summarize time-to-event data. Graphical data displays may also be used to summarize the data.

For analysis purposes, the data from subjects receiving rivaroxaban in Part A of the study will be combined with the data from subjects in Part B of the study randomized to rivaroxaban. The data

will also be summarized separately for subjects randomized in Part B only (rivaroxaban vs. ASA), and for subjects participating in Part A only.

All CIAC adjudicated efficacy and bleeding outcomes will be used in the final analyses.

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

2.1 Definition of Trial Dates

Trial reference start date is defined as the date on which the first dose of study drug is taken by 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:

- Date of the last study-related visit or phone contact (including scheduled or unscheduled visits)
- Date of the last study-related procedure, finding or event, 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. Due to the nature of Part A, the first dose date for Part A subjects will not be allowed to be missing. For Part B randomized subjects, 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. 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 the randomization date if day and month are missing.

Last dose date is defined as the date on which the last 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 will be set to the latest logically possible date. It will be capped by (that is, taking the minimum with) Day 353 date, death date, trial reference end date, and the upper bound of the logically possible range if partial date is available, and further bounded below by (that is, taking the maximum with) the (imputed) first dose date, any complete temporary drug stop and re-start date, or the lower bound of the logically possible range.

Last efficacy-evaluation date is defined as the date of the last study visit at which the outcome status of efficacy endpoints is evaluated – Month 12 or ESMD visit.

Planned treatment end date: 12 months since randomization or enrollment for each subject. The planned treatment end date varies for subjects depending on their randomization or enrollment date.

2.2 Analysis Sets

Full Analysis Set: This analysis set consists of all subjects in Part A who receive at least 1 dose of study drug and all subjects in Part B who are randomized and receive at least 1 dose of study drug.

Safety Analysis Set: This is the same as Full Analysis Set.

Per-protocol Set: The per-protocol set will exclude subjects with key protocol deviations from full analysis set. These deviations will include the following:

- Not meeting the following key inclusion or exclusion criteria:
  - INT-1: inclusion criteria 1, exclusion criteria 1, 4, 6 (> 90 consecutive days), 7, 8, 13, 14, 15, 18
  - INT-2: inclusion criteria 1, exclusion criteria 1, 4, 6 (> 90 consecutive days), 7, 8.1, 13, 14, 15, 18
- Taking incorrect study drug
- Not discontinuing study drug permanently according to the protocol
- Having been taking prohibited concomitant therapies as specified in the protocol

PK Analysis Set: All subjects who receive at least 1 dose of study drug and have quantifiable rivaroxaban plasma concentrations will be included in the descriptive PK analysis.

PD Analysis Set: All subjects who receive at least 1 dose of study drug and have quantifiable and time-matched PT, aPTT, and/or anti-FXa activity values will be included in the descriptive PD analysis.

2.3 Analysis Periods

On-Treatment Period: This analysis period includes all data from the first dose of study drug to 2 days after the last dose of the study drug administration (inclusive).

Up-to-End-of-Treatment Period: This analysis period includes all data from first dose to end of treatment visit (i.e., last efficacy-evaluation date - Month 12 or ESMD visit)

Up-to-Last-FU (last contact): This analysis period includes all data from first dose to trial reference end date.

2.4 Definition of Subgroups

Descriptive summaries of efficacy and safety may be done by considering the following subgroups:

- Age groups
- Sex
- Race
- Ethnicity
- Geographic region
- Baseline Creatinine Clearance (CrCl)
- Weight groups
- Type of antiplatelet/anticoagulant therapy prior to enrollment
- Others (e.g., use of central venous lines for > x days, and other parameters related to baseline characteristics of Fontan population – to be specified in the DPS)

3. SUBJECT INFORMATION

Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented by treatment. Frequency tables for qualitative data will be provided. No statistical tests will be performed to compare these characteristics across treatment groups. Unless stated otherwise, all subject information summaries will be based on safety analysis set and will be presented for rivaroxaban combined from Parts A and B, ASA and rivaroxaban from Part B, and rivaroxaban from Part A.

3.1 Enrollment and Medical History

Enrollment, screen failures, and inclusion/exclusion criteria will be summarized for all screened subjects.

Medical history findings will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) by Primary System Organ Class / High Level Term.

Type and other relevant information of the Fontan procedure performed will be summarized (details specified in the DPS).

3.2 Demographics and Baseline Characteristics

Descriptive statistics by treatment group will be provided for the baseline demographics and disease characteristics.

3.3 Disposition Information

The number of subjects and the reasons for premature discontinuation of study treatment will be summarized by treatment group as recorded on the eCRF.

The distribution of time from enrollment into the study to early discontinuation will be shown by KM plot.

A subject will be considered to have completed the study if the subject completes:

- The Follow-Up Contact 30 days after the last dose of study drug taken for subjects who complete the 12 month treatment
- The ESMD Month 12 Follow-Up for subjects who discontinue the study drug prematurely

Available vital status at the planned treatment end period (Month 12) will be summarized for subjects who prematurely discontinued the study or were lost to follow up.

3.4 Treatment Compliance

Rivaroxaban will be administered twice daily in an open-label fashion. Rivaroxaban will be taken in the morning and in the evening (approximately 12 hours apart) as described in study booklet.

Subjects randomized to ASA will receive approximately 5 mg/kg as a single dose. ASA will be provided as tablets according to the local practices.

Dose adjustments due to increased body weight will be made at Month 6 for subjects in Parts A and B for both rivaroxaban and ASA.

IWRS will keep track of study drug dispensed to subjects in both Part A and Part B. Study drug accountability will be performed at each visit.

For each subject, the treatment compliance rate is estimated as follows

Compliance rate (%) = 100 * actual treatment duration / intended treatment duration

More specifically, the actual treatment duration will be calculated by minimum of [Day 353 date, last dose date, death date, and the first primary efficacy outcome date] - first dose date + 1 - dose interruption days. The intended treatment duration will be calculated by minimum of [Day 353 date, death date, and the first primary efficacy outcome date] - first dose date + 1 - dose interruption days due to the reasons specified in protocol 10.2.1 (for example, bleeding, and other AEs).

Compliance rate will be summarized by treatment group.

3.5 Duration of Exposure

Duration of treatment exposure is defined as the duration between the first dose date and last dose date, inclusive. Note that temporary study drug interruption is not excluded from this definition. Duration of treatment exposure will be summarized by treatment group.

Number of patients who had interruptions and total interruption days will be summarized by treatment group.

3.6 Protocol Deviations

Major protocol deviations will be summarized by treatment group. The categories of protocol deviations may include, but are not limited to the following:

- Not meeting key inclusion or exclusion criteria
- Taking incorrect study drug
- Not discontinuing study drug permanently according to the protocol
- Having been taking prohibited concomitant therapies as specified in the protocol

3.7 Prior and Concomitant Medications

Medications received prior to the first dose of study drug are considered prior medications, even if the subject continued on the medication concomitantly with the study drug.

- The number and percentage of subjects who received prior medications will be summarized.
- The number and percentage of subjects who received any anticoagulant/antiplatelet medication taken after the Fontan procedure and prior to first dose of study drug will be summarized.

Concomitant medications include all other medications received between the first dose and the last dose of study drug.

- The number and percentage of subjects who received concomitant medications will be summarized.

Separately, anticoagulant/antiplatelet use after the study treatment period (i.e., after stopping study treatment) will be summarized.

All prior and concomitant medications will be summarized using the WHO-DD.

4. SAFETY

No formal hypothesis testing will be performed.

If the date of an outcome event is missing or partially missing, the earliest logically possible date after enrollment will be used as the event date. The date of an outcome event is defined as the maximum of date of enrollment and the first day of the month if only day is missing and is defined as maximum of date of enrollment and the first day of the year if both day and month are missing. Maximum efforts will be undertaken to avoid missing event data.

All missing or partial data will be presented in the subject data listing as they are recorded on the eCRF.

Unless otherwise stated, all safety summaries and analyses will be performed based on the Safety Analysis Set (which is equivalent to Full Analysis Set).

4.1 Bleeding Events

The primary safety outcome is the major bleeding events, as defined below. Clinically relevant non-major bleeding events and trivial (minimal) bleeding will be secondary safety outcomes.

Bleeding events will be adjudicated by the CIAC using the International Society on Thrombosis and Hemostasis (ISTH) recommendations (Buller 2007, Schulman 2005).

Major bleeding is defined as overt bleeding and:

- Associated with a fall in hemoglobin of 2 g/dL or more; or
- Leading to a transfusion of the equivalent of 2 or more units of packed red blood cells or whole blood in adults; or
- Occurring in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; or
- Contributing to death.

Clinically relevant non-major bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with:

- Medical intervention, or
- Unscheduled contact (visit or telephone call) with a physician, or
- (Temporary) cessation of study treatment, or
- Discomfort for the subject such as pain, or
- Impairment of activities of daily life (such as loss of school days or hospitalization).

Trivial (minimal) bleeding is defined as any other overt bleeding event that does not meet criteria for clinically relevant non major bleeding.

The main description will be based on Safety Analysis Set during the On-treatment period (bleeding events confirmed by the CIAC).

Incidence rates (number of subjects with bleeding event during the period divided by the number of subjects at risk at the beginning of the period) and the respective 95% CIs will be calculated for the major and clinically relevant non major bleedings by treatment group. Cumulative

incidence rates (time to first event; Kaplan-Meier) will be calculated for the major bleeding and clinically relevant non-major bleeding.

In addition, listing for all bleedings will be provided, including those that are reported more than 2 days after stop of study medication.

Baseline demographics and disease characteristics relationship to bleeding risk may be explored.

4.2 Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as those adverse events that occur from the first day of study drug to the last day of study drug + 2 days inclusive. Summary of the incidence of the following adverse events will be done:

- Treatment-emergent adverse events
- Treatment-emergent serious adverse events
- Serious adverse events with onset > 2 days from the stop of study drug
- Adverse events leading to permanent study drug discontinuation

In addition, incidences of adverse events by system organ class and dictionary-derived (preferred) term will be provided.

Listings will be done for all Adverse Events, and for all Serious Adverse Events.

Additional summaries, listings, or subject narratives may be provided, as appropriate.

For subjects who are not in Safety Analysis Set, AEs will be listed separately.

The ICF is signed at screening, prior to any study related procedure is done. Any AE that a subject develops after the ICF is signed but before the first dose is administered will be reported separately.

4.3 Clinical Laboratory Tests

The study will collect laboratory data at baseline, Month 3 (limited laboratory data at Month 3), and Month 12. Laboratory data will be summarized by treatment group and time point by descriptive statistics.

4.4 Vital Signs and Physical Examination Findings

Vital signs and physical examination findings will be summarized by treatment group and time point.

5. EFFICACY

No formal hypothesis testing will be performed. The primary efficacy outcome will be any thrombotic event (venous or arterial), defined as:

- The appearance of a new thrombotic burden within the cardiovascular system on either routine surveillance or clinically indicated imaging, or
- The occurrence of a clinical event known to be strongly associated with thrombus (such as cardioembolic stroke, pulmonary embolism).

Subjects who develop either a symptomatic or asymptomatic thrombotic event during the study must permanently discontinue study drug. After cessation of study treatment, it is at the investigator's discretion to continue with other antithrombotic therapy. The investigator should document this therapy in the electronic case report form (eCRF). All available imaging results, e.g., transthoracic or transesophageal echocardiograms, or MRIs, relevant to a suspected thrombotic event should be sent to the CIAC for event adjudication. Thrombotic events will not be reported as adverse events or serious adverse events, as they will be reported as efficacy outcomes.

Transthoracic Echocardiograms will be obtained at screening, at Month 6 and Month 12 for the assessment of thrombotic events. For subjects who prematurely discontinue study drug for any reason (except when the child is enrolled because the local reader reviews the screening echo as without thrombosis and later on the central reviewer reports the presence of a thrombus), the final echocardiogram will be performed as soon as possible after discontinuation, at the ESMD visit. Investigators can image as often as medically necessary or as needed based on their institution's standard of care; however, protocol-based imaging must be performed at screening, Month 6 and at the end of therapy. Echocardiograms will be sent to a core laboratory for blinded reading and to minimize inter-site variability and bias.

The main efficacy description will be based on Full Analysis Set, excluding subjects who start on study drug but are discontinued if central reading by the core laboratory reports thrombosis on the Screening transthoracic echocardiogram (these subjects will be included however in the safety analysis) based on up-to-the-end-of-treatment period (outcomes confirmed by the CIAC).

Events that are reported after Month 12 or ESMD visit will be described in additional summaries or listings.

Additionally, data may also be summarized based on Full Analysis Set and up-to-last-FU (last contact) period or Per-protocol Analysis Set and On-treatment period.

Incidences rates (number of subjects with efficacy event during the period divided by number of subjects at risk at the beginning of the period) and the respective 95% CIs will be calculated for the primary efficacy outcome by treatment group.

Cumulative incidences (time to first event; Kaplan-Meier) will also be calculated for the efficacy outcomes.

In addition, listings of any efficacy outcomes will be provided.

Baseline demographics and disease characteristics relationship to thrombotic risk may be explored.

The numbers and percentages of subjects with missing Follow-Up Contact (30-days after last dose or Month 12) will be summarized.

All missing or partial data will be presented in the subject data listing as they are recorded on the eCRF.

6. PHARMACOKINETICS

Part A

PK and PD blood samples will be collected on the first day of dosing (Visit 2/D1) between 0.5 to 1.5 hours and again between 1.5 to 4.0 hours post-dose. Additional samples will be collected on Day 4 (Visit 2/D4), just prior to dose administration and again between 0.5 to 1.5 hours, 1.5 to 4.0 hours and 6.0 to 8.0 hours post-dose. PK and PD samples will also be taken at Month 3 and Month 12.

All PK and PD samples will be sent to a central laboratory for quantitative analysis.

The plasma PK parameters determined will be AUC_{0-24} and C_{max} after a single dose and at steady-state AUC_{0-24ss}, C_{maxss} and C_{minss}. The PT and aPTT will be used to assess the PK/PD relationship after administration of the study drug.

Part B

PK and PD blood samples will be collected on the first day of dosing (Visit 2/D1) up to 3 hours prior to the AM dose, between 0.5 to 1.5 hours and again between 2.5 to 4.0 hours post-dose. PK and PD samples will also be taken at Month 3 and Month 12.

All PK and PD samples will be sent to a central laboratory for quantitative analysis.

The plasma PK parameters determined will be AUC_{0-24} and C_{max} after a single dose and at steady-state AUC_{0-24ss}, C_{maxss} and C_{minss}. The PT, aPTT, and anti-FXa activity (AXA) will be used to assess the PK/PD relationship after administration of the study drug when data are available.

Both Parts

Descriptive statistics will be used to summarize rivaroxaban PK data for each time interval and the concentration-time profile will also be described. PD measurements, including PT, aPTT, and AXA will be plotted against rivaroxaban plasma concentrations and will also be summarized by timepoint when data are available.

Rivaroxaban PK parameters including AUC_{0-24ss}, C_{maxss}, and C_{minss} at steady date will be derived by model-based methods.

The subject's steady-state AUC_{0-24ss} will also be evaluated if it matches with that of the reference AUC_{0-24ss} after 10 mg total daily dose at steady-state (Refer to Figure 2, Pharmacokinetic Decision Tree). C_{maxss} and C_{minss} at steady-state might also be compared numerically with those in adult patients. PK/PD relationship will be explored in pediatric subjects.

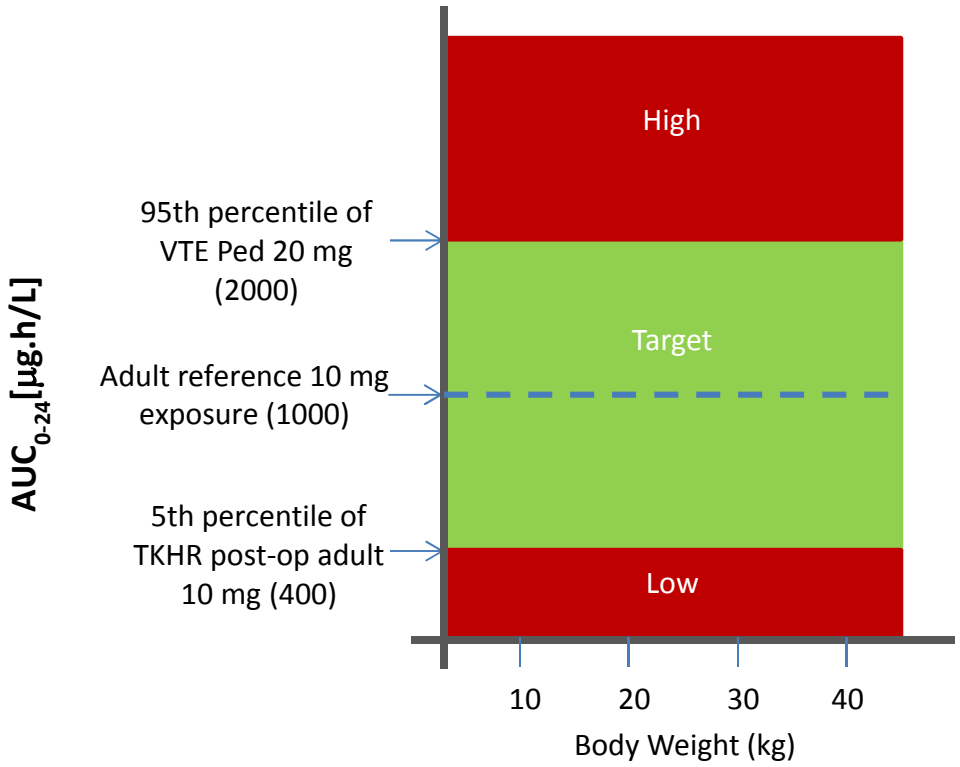
PK and PD Analysis datasets will be respectively used for summaries of PK and PD parameters.

PK/PD data analysis plan (DAP) will be provided separately before database lock (DBL). Results from PK and PK/PD analyses will be reported separately from the Clinical Study Report.

7. HEALTH ECONOMICS

There are no plans to collect health economics data.

Figure 2: Pharmacokinetic Decision Tree



VTE = venous thromboembolism; ped = pediatric; post-op = post-operative; TKHR = total knee or hip replacement
Rivaroxaban exposure (steady-state AUC_{0-24}ss) in target (green) zone according DRC recommendations for individual subjects at steady-state;

8. REFERENCES

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