Janssen Scientific Affairs, LLC

Statistical Analysis Plan

Multicenter Trial of Rivaroxaban for Early Discharge of Pulmonary Embolism from the Emergency Department

MERCURY PE

Protocol 39039039APE4001; Phase 4

JNJ-39039039; BAY 59-7939 (rivaroxaban)

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

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
ACTS	Anti-Clot Treatment Scale
CEC	Clinical Endpoints Committee
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
ED	Emergency Department
eCRF	Electronic Case Report Form
EOS	End of Study/early withdrawal
ISTH	International Society on Thrombosis& Haemostasis
ICH	International Conference on Harmonization
INR	International Normalized Ratio
ITT	Intention-to-Treat
IWRS	Interactive Voice Response System
LOS	Length of Stay
MPD	Major Protocol Deviation
PE	Pulmonary Embolism
PRO	Patient Report Outcome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
VTE	Venous Thromboembolism

AMENDMENT HISTORY

SAP (VERSION 2.0)

The original Statistical Analysis Plan (first version) was finalized and issued on 27 January 2016. All changes and clarifications of planned analyses in the SAP Version 2.0 (since the original SAP was issued) are listed below:

Topic or Section	Description of Changes and Clarifications of Planned Analyses
2.3.4. Extent of Exposure	The following paragraph The drug compliance (%) for subjects randomized to receive rivaroxaban is calculated using the following formula • Drug compliance (%) = 100 x (number of pills dispensed – number of pills returned) /treatment duration. was replace by Subjects who randomized to rivaroxaban take an initial dose of 15 mg orally twice daily for the first 21 days. The drug compliance (%) for this period is calculated using the following formula • 100 x (number of tablets taken during 15 mg BID part divided by 2) / (date of the last study drug administration of 15 mg BID part - date of the first study drug administration+1). After first 21 days, subjects who randomized to rivaroxaban take dose of 20 mg orally once daily. The drug compliance (%) for this period is calculated using the following formula • 100 x (number of tablets taken during 20 mg QD part) / (date of the last study drug administration - date of the first study drug administration of 20 mg QD+1). The overall drug compliance (%) is calculated using the following formula • 100 x (number of tablets taken during 15 mg BID part divided by 2 + number of tablets taken during 20 mg QD part) / (date of the last study drug administration - date of the first study drug administration+1).
2.3.10 Analyses for Secondary Endpoints	Deleted analyses at Day 3.

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis populations, derived variables and statistical analysis methods.

1.1. Trial Objectives

Primary Objective

The primary objective of the study is to demonstrate that low risk PE patients who are discharged from the ED to the home environment and treated with rivaroxaban as outpatients have fewer total days in the hospital for bleeding and/or venous thromboembolism (VTE) events through Day 30 compared to patients who are treated with initial hospitalization and standard-of-care.

Secondary Objective

The secondary objective of the study is to assess the reoccurrence of symptomatic, objectively confirmed VTE, defined as recurrent PE or new or recurrent DVT (including symptomatic upper extremity DVT) or VTE related death within 90 days of randomization.

Exploratory Objective

The exploratory objective of this study is to evaluate patient outcomes by baseline risk factors

1.2. Trial Design

This is a randomized, open-label, parallel-group, multicenter study conducted in the United States (US). Eligible subjects will include men and women, 18 years of age and older, who have a confirmed diagnosis of acute symptomatic PE with or without symptomatic DVT. Approximately 300 PE subjects presenting to the ED and assessed as being at low risk of clinical deterioration using the Hestia criteria will be randomized in a 1:1 ratio to one of two treatment strategies: 1) rivaroxaban and discharge from the ED to the home environment or 2) standard-of-care (as per local protocol and defined by the medical team caring for the subject). All subjects will be followed for 90 days after starting randomized treatment. Subjects meeting all inclusion and no exclusion criteria will be eligible for enrollment.

The study consists of a Screening and Randomization Period, followed by a 90-day open-label treatment period, and an end-of-study/early withdrawal (EOS) visit. The duration of study participation for each subject is approximately 3 months.

Subjects will undergo screening in the ED and must be randomized within 12 hours after the confirmation of PE diagnosis. All bleeding events (ISTH major and clinically relevant non-major bleeding events), efficacy events (VTE related death, recurrence of PE or new or recurrent DVT) and all deaths during the study will be adjudicated in a blinded manner by a Clinical Endpoints Committee (CEC). Events will be adjudicated throughout the entire 90 days of randomized treatment. The CEC will independently review clinical events data as they become available, and will adjudicate and will classify deaths, bleeding events, and recurrence of PE and new or recurrent DVT in a consistent and unbiased manner.

An independent Data Monitoring Committee (DMC) will monitor the progress of the study and will ensure the safety of study subjects. An Executive Committee will review recommendations from the DMC regarding safety analyses and/or study modifications and will oversee implementation, if necessary, of these study modifications. In addition a Study Coordinator Operational Committee will provide input to the operational logistics regarding study design and conduct of the study.

The frequency and timing of efficacy, safety, and other measurements are provided in Time and Events Schedule in the study protocol.

1.3. Hypotheses for Trial Objectives

Clinical:

The clinical hypothesis is that an early discharge strategy for low risk PE patients, identified in the ED, and discharged to the home environment and treated with rivaroxaban as outpatients will result in fewer days in the hospital for bleeding and/or VTE events through Day 30 than patients treated with standard-of-care.

Safety:

The safety hypothesis is that major bleeding rates as assessed by the International Society on Thrombosis and Haemostasis (ISTH) criteria at 90 days of randomized treatment will be similar between the rivaroxaban and standard-of-care strategies.

1.4. Sample Size Justification

Following pragmatic considerations, the sample size for this study was determined using assumptions related to the expected number of days of initial inpatient hospitalization (beginning from randomization to discharge from the hospital) and any subsequent hospitalization(s) related to bleeding and/or VTE events up to 30 days. A large-sample confidence interval (CI) approach was used to determine the sample size required for estimating the difference in mean length of stay between the two randomized groups. From Aujesky et al. 2011 (see protocol for details); the standard deviation is 1 day for the outpatient group and 3.1 days for the inpatient group from the initial hospital stay. From the available data, the average number of days of hospitalization after discharge is less than 2 days and the percentage of patients with VTE related hospitalization is less than 5%. With this information, the contribution from VTE related hospitalization after discharge has a very small impact on the standard deviations received from the initial hospital stays which were used in the sample size calculation. A total of a 150 subjects per group will provide a two-sided 95% CI with about a 0.5 day of margin of error. The margin of error is defined as the quantity from the observed difference in means to the end point of the CI.

The above sample size estimate will also allow an examination of the difference in the recurrence of VTE events in the 2 randomized groups. The incidence of recurrent VTE events is generally low and largely infrequent among low-risk PE patients. In the Aujesky et al. 2011

study, the 90-day recurrence rates of VTE among both inpatients and outpatients were reported to be less than 1% (with a 95% upper confidence limit = 2.7%).

1.5. Randomization and Blinding

The principle purpose of randomization is to ensure unbiased treatment assignment in a manner that assures minimum allocation bias, and balancing both known and unknown prognostic factors at the baseline. Subjects will be randomly assigned in a 1:1 ratio to the outpatient group to receive rivaroxaban or to the inpatient group to receive standard-of-care. The treatment assignment is based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by study centers. As this is an open label study, blinding procedures are not applicable.

2. ANALYSES PLANNED

2.1. General Analysis Definitions

2.1.1. Visit Windows

Two study periods are defined as follows:

- Randomization to visit two
- Visit two to the end of study

Data collected from different study periods are analyzed accordingly.

2.1.2. Pooling Algorithm for Analysis Centers

Small centers may be pooled if the analyses are stratified by centers.

2.1.3. Start and End of Study Periods

The trial termination date will be the completion date of the entire trial. The trial reference start date/time for a subject will be the date/time of randomization of the subject. The trial reference end date for a subject is the date of the last trial-related procedure for the subject and is defined as the maximum of

- Date of last visit (scheduled or unscheduled visit; Early Study
- Medication Discontinuation Visit/End of Study Visit)
- Date of the last study medication

2.1.4. Study Day

When needed, the following definitions of Study Day can be used. For each subject, each day during the trial will be assigned a Study Day with respect to the trial reference start date which is the date of randomization of the subject.

- Study Day = Assessment date – trial reference start date + 1; if assessment date ≥ trial reference start date
- Study Day = Assessment date - trial reference start date; if assessment date < trial reference start date.

2.1.5. On Treatment

A study subject is considered to be on treatment during the period from the first study medication administration (instead of randomization) to the Minimum (Earliest) of [Trial end date/time, Date/time of Death, Date/time of the last study medication administration + 2 days], which is defined as the end of being on-treatment. A safety endpoint event or safety abnormality (of clinical laboratory or vital signs) is considered to occur while on treatment if its onset date/time (complete or missing/incomplete) is logically possible to be within the on treatment period.

2.2. Analysis Sets

For the purpose of statistical analyses, 2 analysis sets will be considered:

- Intention-to-treat (ITT) analysis set: The intention to treat analysis set includes randomized subjects who meet trial enrollment criteria. Screen Failure patients who were randomized in error are not included in ITT.
- Safety analysis set: The safety population includes all randomized subjects who take at least 1 dose of study drug.

2.2.1. ITT Analysis Set

All analyses, except safety analyses, are based on the intention-to-treat (ITT) analysis set for this study.

2.2.2. Safety Analysis Set

Any safety measures will be summarized using safety population.

2.2.3. Pharmacokinetics Analysis Set

No PK data will be collected for this study.

2.2.4. Definition of Subgroup

Centers may be considered as subgroups.

2.3. Methods of Analysis

2.3.1. Hypotheses for Analyses

For detailed clinical and safety hypotheses, see Section 1.3.

2.3.2. Demographics and Baseline Characteristics

Descriptive statistics (such as mean, standard deviation, median, minimum and maximum) by treatment group will be provided for continuous variables such as age, weight, and height. Counts and (appropriate) percentages by treatment group will be provided for categorical variables such as sex and race.

2.3.3. Discontinuation/Completion Information

Incidences and percentages of discontinuations from the study in different study periods will be provided by treatment group. Time to discontinuation may be summarized by treatment group using the Kaplan-Meier method depending on the rate of discontinuation. Subjects who complete the study will be censored at the time of the end of study.

2.3.4. Extent of Exposure

The following treatment duration will be calculated:

- Treatment duration (including days off study drug) = Date of the last study medication administration - date of the first study medication administration + 1

Subjects who randomized to rivaroxaban take an initial dose of 15 mg orally twice daily for the first 21 days. The drug compliance (%) for this period is calculated using the following formula

- 100 x (number of tablets taken during 15 mg BID part divided by 2) / (date of the last study drug administration of 15 mg BID part - date of the first study drug administration+1).

After first 21 days, subjects who randomized to rivaroxaban take dose of 20 mg orally once daily. The drug compliance (%) for this period is calculated using the following formula

- 100 x (number of tablets taken during 20 mg QD part) / (date of the last study drug administration - date of the first study drug administration of 20 mg QD+1).

The overall drug compliance (%) is calculated using the following formula

- 100 x (number of tablets taken during 15 mg BID part divided by 2 + number of tablets taken during 20 mg QD part) / (date of the last study drug administration - date of the first study drug administration+1).

2.3.5. Protocol Deviations

Major protocol deviations (MPD) will be summarized (or provided by a listing if the number of MPD is too small) by treatments. Definitions of major protocol deviations based on data reviews will be provided in this study SAP, and will be finalized before the database lock.

2.3.6. Previous Medications

For the safety population, the number and percentage of subjects who receive medications prior to first study medication administration will be summarized. A concomitant medication record is considered as previous medication if

- The earliest logically possible start date of the medication < date of first study medication administration.

2.3.7. Concomitant Medications

For the safety population, the number and percentage of subjects who receive concomitant medications during the treatment period (between the first and last study medication administrations) will be summarized. A medication record will be considered concomitant medication during the treatment if both of the following conditions are met:

- The earliest logically possible start date of the medication ≤ date of the last study medication administration
- The latest logically possible stop date of the medication ≥ date of the first study medication administration, or stop date of the medication is "continuing".

2.3.8. Concomitant Medications Start during the Trial

A concomitant medication record will be considered concomitant medication started during the treatment if:

- The earliest logically possible start date of the concomitant medication > date of the earliest study medication administration, and < date of the last study medication administration.

2.3.9. Analysis for Primary Endpoint

The primary analysis will be based on ITT analysis set. All statistical tests will be based on the 0.05 alpha level of significance (2-sided). No adjustments in the Type 1 error for multiplicity will be made.

2.3.9.1. Primary Endpoint

The primary clinical endpoint is the number of days of initial inpatient hospitalization (beginning from randomization to discharge from the hospital) plus any subsequent hospitalization(s) related to bleeding and/or VTE events up to 30 days.

2.3.9.2. Analysis for Primary Endpoint

The primary endpoint will be calculated for each subject. A two-sided 95% CI will be calculated for the mean difference of length of stay (LOS) in hospital from 2 treatment groups. No testing for the primary hypothesis will be performed.

2.3.10. Analyses for Secondary Endpoints

The secondary analyses will be based on ITT analysis set.

2.3.10.1. Secondary Endpoints

The following secondary endpoints will be analyzed

- Reoccurrence of symptomatic objectively confirmed VTE, defined as recurrent PE or new or recurrent DVT (including symptomatic upper extremity DVT) or VTE related death within 7,14,30 and 90 days of randomization.
- Number of unplanned hospital or physician office visits for VTE symptoms and/or bleeding through 90 days.
- Length of initial and subsequent hospitalization(s) for any reason through Day 90.

2.3.10.2. Analyses for Secondary Endpoints

All secondary endpoints will be summarized.

A right-sided 95% CI will be calculated, using EXACT method (for example, a procedure similar to StatXact 9 with exact option), for the difference (the proportion of rivaroxaban minus the proportion of standard care) of event rates of reoccurrence of symptomatic, objectively confirmed VTE, defined as recurrent PE or new or recurrent DVT (including symptomatic upper extremity DVT) or VTE related death within 90 days of randomization. The same procedure may be applied to the reoccurrence of VTE at Day 7, 14 and Day 30 when appropriate.

A two-sided 95% CI, based on large sample normal approximation, will be calculated for the difference of the rates of unplanned hospital or physician office visits for VTE symptoms and/or bleeding through 90 days.

Under the assumption of normal distribution, a two-sided 95% CI will be calculated for the difference in length of initial and subsequent hospitalization(s) for any reason through Day 90.

2.3.11. Analyses for Safety Endpoints

The secondary analyses will be based on safety analysis set.

2.3.11.1. Safety Endpoints

The primary safety endpoint is ISTH major bleeding at Day 90; these events will be adjudicated by CEC. The secondary safety endpoints include:

- VTE related death within 90 days of randomization
- Clinically relevant non-major bleeding
- Minimal bleeding
- Overall safety defined as a composite of ISTH major bleeding, clinically relevant non-major bleeding, and mortality.

Clinically relevant non-major bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician (temporary) cessation of study treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life.

Minimal bleeding is defined as all other overt bleeding episodes that do not meet the ISTH criteria for major or clinically relevant non-major bleeding.

All safety endpoints will be summarized or listed by treatment groups. The 95% CI for the difference of event rates between treatments may be provided when appropriate.

2.3.11.2. Analyses for Adverse Events

The original terms used in the CRFs by investigators to identify AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment Emergent Adverse Event

Treatment emergent adverse event (TEAE) is defined as an adverse event starting between the first study medication administration and 2 days after the last study medication administration during the treatment period, or an event that starts before the first study medication but it is worsening during above mentioned period.

Specific Definition

A TEAE flag will be created in the analysis dataset as specified below:

- When the onset date is complete:
  The AE will be flagged as TEAE if the onset date ≥ the date of the first study medication administration AND ≤ 2 days after the last study medication administration
- When the onset date of the AE is incomplete/missing:
  The TEAE will be determined on a case-by-case basis.

Duration of Adverse Event

For the computations of duration in days of a TEAE or duration in days of an AE, the following approach will be used (which is based on date but not time):

- Duration of AE = Latest logically possible AE resolution date – earliest logically possible AE onset date + 1.

Summaries of Adverse Events

Unless stated otherwise, all summaries of adverse events (AE) will be provided by system organ class and dictionary-derived (preferred) term. A total column will be included in all safety summaries. The number and percentage of subjects with TEAEs and Treatment-emergent Serious Adverse Events (TESAE) will be summarized for each treatment group by system organ class and dictionary-derived term. Event rates of TEAEs and TESAEs will also be provided.

All AEs are coded using MedDRA, Version 15.1.

2.3.12. Patient-Reported Outcomes

Anti-Clot Treatment Scale (ACTS)

At follow-up visits Day 14, Day 30, and Day 90, treatment satisfaction will be assessed using a validated measure for treatment satisfaction: the Anti-Clot Treatment Scale (ACTS). It includes a 12-item (items 1 to 12) ACTS Burdens scale and a 3-item (items 14 to 16) ACTS Benefits scale.

The item 13 is the assessment for overall burden, and the item 17 is the assessment for overall benefit. The scores range from 'Not at all' to 'Extremely' on a five-point Likert scale (psychometric rating).

All items will be summarized by treatment arms. Items 13 and 17 will be compared between treatment groups assuming the averages of the scores are approximated normally distributed.

Site-of-Care Satisfaction Questionnaire

The Satisfaction to Site-of-Care questionnaire (standard-of-care versus early discharge on rivaroxaban therapy) will be administered after 7 days on anticoagulant therapy (See Attachment 4 of the protocol).

Satisfaction to Site-of-Care (hospitalization versus home care) rates the patient's level of satisfaction to care and location with care received as well as preference to location of care provided. Patients rate 2 items of this scale of 1=Very satisfied; 2=Quite satisfied; 3=Neither; 4=Quite dissatisfied; and 5=Very dissatisfied for satisfaction questions and for the one preference question responses include 1=In the hospital; 2=In the community; and 3=No preference.

All items will be summarized. The first two items will be compared between treatment groups assuming the averages of the scores are approximately normally distributed.

2.3.13. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the eCRF for all subjects throughout the study. Length of initial and subsequent hospitalizations as well as, all-cause and VTE related re-hospitalizations due to recurrence will be economically evaluated.

2.3.14. Time to Onset of Events

Time to onset of an event may be calculated. The events of interest may include major bleeding and first VTE related re-hospitalizations. The distributions of time to onset of event observed from the 2 treatment groups will be estimated using the Kaplan Meier method. However, if the number of events is too small, a listing will be provided without using the KM method. Treatments will be compared using a log-rank test when appropriate (depending on the number of events).

2.3.15. Subgroup Analyses

The only potential subgroups are study centers. There is no subgroup analysis planned at this time.

2.3.16. Clinical Laboratory Tests

Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be provided for each laboratory analyte at baseline. A clinical laboratory test value is considered abnormal if it is outside the reference range.

2.3.17. Vital Signs

Summaries by treatment group for the observations and changes from baseline to the last observation (excluding baseline) for the vital sign parameters will be provided.

2.3.18. Electrocardiogram

Summaries by treatment group for the ECG parameters will be provided.

2.4. Interim Analysis

There is no interim analysis planned for this study.