SYNOPSIS

Name of Sponsor/Company	Janssen Scientific Affairs*
Name of Investigational Product	JNJ-39039039; BAY 59-7939 (Rivaroxaban)

* Janssen Scientific Affairs, LLC is a global organization that operates through different legal entities in various countries. The term "sponsor" is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved
Date: 17 January 2017
Prepared by: Janssen Scientific Affairs

Protocol No.: 39039039NAP1004

Title of Study: Randomized, Parallel-Group, 2-Part Study to Assess the Independent Effects of 4-Factor Prothrombin Complex Concentrate and Tranexamic Acid on Bleeding Parameters and Pharmacodynamics After a Punch Biopsy Procedure in Healthy Subjects Treated With Rivaroxaban

NCT No.: NCT02561923

Clinical Registry No.: CR107832

Principal Investigator: Barbara K, Lomeli, MD, [redacted], USA

Study Center: Single-center study

Publication (Reference): None

Study Period: 04 September 2015 to 17 June 2016

Phase of Development: 1

Objectives:

The primary objectives of this 2-part study in healthy subjects were to assess the independent effects of both a 4 Factor Prothrombin Complex Concentrate (PCC, Kcentra®) and tranexamic acid (TXA) on (1) the bleeding parameters bleeding duration (BD) and bleeding volume (BV), following a punch biopsy, and (2) their effects on the anticoagulant/pharmacodynamic (PD) (prothrombin time [PT] and endogenous thrombin potential [ETP]) changes induced by rivaroxaban at steady state to better understand their potential role in bleeding reversal.

Part 1: The primary objective was to determine the sensitivity and variability of the bleeding parameters (BD and BV) after the punch biopsy procedure following a single 20-mg dose of rivaroxaban.

The secondary objective was to assess the pharmacokinetics (PK) and PD of rivaroxaban. The safety and tolerability of rivaroxaban were also evaluated.

Part 2: The primary objective was to assess the effects of both Kcentra and TXA on the bleeding parameters (BD and BV) and PD (PT and thrombin generation assay [TGA]) of rivaroxaban at steady state.

The secondary objective was to assess the PK at steady state. The safety and tolerability of rivaroxaban were also evaluated.

The exploratory objectives were to assess the effects of both Kcentra and TXA on the levels of coagulation factors (FII, FVII, FIX, FX, Protein C and Protein S) and biomarkers reflective of increased thrombin generation including prothrombin fragment 1+2 (F1+2), D-dimer, and thrombin-antithrombin complex (TAT).

Methodology:

This was a 2-part, single-center study conducted in healthy men and women.

Part 1, an open-label portion of the study, established the punch biopsy procedure and assessed the model's sensitivity and variability of the bleeding parameters (BD and BV) after a single 20-mg dose of rivaroxaban. This part consisted of a Screening Phase (Days -29 to -2), a 3-day treatment period, and an end-of-study/early withdrawal visit on Day 8.

Part 2 was a randomized, 3-treatment, double-blind, parallel-group design, that assessed both the bleeding and PD reversal effects of Kcentra and TXA with a saline control, after receiving a supratherapeutic 20-mg twice-daily dose regimen of rivaroxaban. Part 2 consisted of a Screening Phase (Days -29 to -2), an 8-day treatment period (Days -1 to 7), and an end-of study/follow-up visit on Day 11.

An analysis of preselected data was performed after the completion of Part 1 and prior to the initiation of Part 2 to assess the sensitivity and variability of the bleeding parameters (BD and BV) of the model. In addition, interim assessments of the blinded results for the BD and BV bleeding parameters were conducted after 25% (N=36) and 50% (N=72) of the subjects had completed Part 2 of the study, as a continued assessment of the variability of these parameters.

Number of Subjects (planned and analyzed):

Planned: A total of 12 subjects in Part 1 and 144 subjects in Part 2 (48 subjects in each treatment group) were planned to be enrolled.

Analyzed: A total of 12 subjects were enrolled in Part 1 (rivaroxaban monotherapy) of the study. A total of 147 subjects were enrolled in Part 2 of the study, 49 subjects each in Treatment Group A (rivaroxaban 20 mg + Kcentra 50 IU/kg → TXA saline control), B (rivaroxaban 20 mg + Kcentra saline control → TXA 1.0 g), and C (rivaroxaban 20 mg + Kcentra saline control → TXA saline control), respectively. Of the total 147 subjects, 145 (98.6%) subjects completed the study.

Diagnosis and Main Criteria for Inclusion:

Healthy men or women, 18 to 55 years of age (inclusive), with a body mass index (BMI) between 18 and 30 kg/m² (inclusive), and a body weight between 50 and 100 kg were included in the study. Subjects must have had coagulation test results of PT and activated partial thromboplastin time (aPTT) within normal limits at study entry. Female subjects were to be postmenopausal or using a medically acceptable method of contraception. Subjects were to have neither a history of nor current significant medical illness or any other hematologic disease (eg, inherited or acquired thrombophilia, bleeding diathesis, etc.).

The 12 subjects from Part 1 were not to be enrolled in Part 2.

Test Product, Dose and Mode of Administration, Batch No.:

Part 1: Rivaroxaban 20-mg dose was administered orally once, within 30 minutes after the start of the standardized meal, on Day 1.

Part 2: Rivaroxaban 20-mg dose administered orally twice daily (every 12 hours) on Days 1 to 3 with a final dose administered on the morning of Day 4. Each dose of rivaroxaban was administered within 30 minutes after the start of the standardized meal (Batch No. [4371399, 4371460] and expiration date [October 2016]).

Reference Therapy, Dose and Mode of Administration, Batch No.:

The below were administered as sequential treatments in Part 2:

***Treatment Group A*:** Kcentra 50 IU/kg, single dose, intravenously administered maximum rate of 210 IU/minutes) on Day 4 (Kcentra → TXA saline control) (1000 U Batch No.: E1160111A; Expiration Date: April 2018);

***Treatment Group B*:** TXA, 1.0 g single dose, intravenously administered (over 10 minutes) on Day 4 (Kcentra saline control → TXA) (Cyklokapron 1000mg/10 mL [100 mg/mL] Batch No.: 44882, Expiration Date: April 2016; Batch No.: 37662, Expiration Date: September 2017);

***Treatment Group C*:** Saline, single dose, intravenously administered on Day 4 (Kcentra saline control → TXA saline control) (Batch No.: 51-809-FW, Expiration Date: March 2017; Batch No.: 52-027-JT, Expiration Date: May 2017).

Duration of Treatment:

Part 1: The total study duration for subjects enrolled in Part 1 (assuming a 28-day Screening Phase, a 3 day treatment period, and a follow-up visit on Day 8) was 37 days.

Part 2: Similarly, the total study duration for subjects enrolled in Part 2 (assuming a 28-day Screening Phase, an 8-day treatment period, and End-of-Study procedures performed at Day 11 was 40 days.

Criteria for Evaluation:

Bleeding Parameters

A punch biopsy procedure was conducted to measure BD and BV. In Part 1, the procedure occurred on Day -1, at the discretion of the Investigator, and no earlier than 4 hours and no later than 4 hours 15 minutes after rivaroxaban administration on Day 1. In Part 2, the procedure occurred on Day -1, at the discretion of the Investigator, and no earlier than 4 hours and no later 4 hours 15 minutes after rivaroxaban administration, and no more than approximately 30 minutes following the completion of Kcentra (or saline control) and approximately 15 minutes following the completion of the TXA (or saline control) on Day 4.

Pharmacokinetic/Pharmacodynamic

The PK and PD samples up to 24 hours were collected at the same timepoints for both Part 1 and Part 2.

Part 1: Serial blood samples were collected for PK (measurement of plasma rivaroxaban concentrations and PK parameters [C_{max}, C_{min}, C_{trough}, t_{max}, and AUC_{τ}]) and PD parameters (PT and TGA) before and up to 24 hours after rivaroxaban administration on Day 1.

Part 2: Blood samples were collected before each dose of rivaroxaban on Days 1 through 3 for the determination of predose and trough rivaroxaban steady-state plasma concentrations, respectively. Serial blood samples were collected for PK and PD before and up to 72 (for PK) and 168 (for PD) hours after the last dose of rivaroxaban on Day 4.

Biomarkers (Exploratory)

Part 1: No biomarker assessments were collected in Part 1.

Part 2: Blood samples were collected for exploratory biomarker assessments (coagulation proteins FII, FVII, FIX, FX, Protein C, Protein S, F1+2, D-dimer, and TAT) on Day -1 (baseline) and on Day 4 before and up to 168 hours after rivaroxaban dose administration.

Safety

Safety and tolerability were evaluated throughout the study. Safety evaluations were based upon the incidence, type and severity of adverse events (AEs) reported throughout the study, changes in clinical laboratory test values (hematology, biochemistry, and coagulation parameters), vital sign measurements, 12-lead electrocardiogram (ECG), and physical examination (including weight and height).

Statistical Methods:

Sample Size Determination

Part 1: The planned sample size of 12 subjects was not based on formal sample size calculations and allowed for the determination of the variability of BD and BV bleeding parameters and clinical judgment of safety and tolerability of the punch biopsy procedure. The intra-subject coefficient of variation (CV) of 25% for BD and 57% for BV were estimated based on the results obtained from Part 1. The BD was selected as the primary endpoint in Part 2 since intra-subject CV associated with BD was lower with BV.

Upon completion of Part 1, the intra-subject CV was estimated to be approximately of 25% for BD and subsequently led to an amendment of the Protocol (Amendment 2).

Part 2: Based on the results obtained from Part 1, and conservatively assuming a 30% intra-subject CV for BD for each treatment group, a sample size of 48 subjects for each treatment group was considered sufficient for the 95% confidence interval (CI) for the BD mean ratio (posttreatment over baseline) to be within 80% to 125% with a power of 80%, assuming that the ratio of the posttreatment over baseline equals 95% or 105%. Additional subjects were to be enrolled to ensure that 48 subjects completed the study in each treatment group. A replacement subject would be the same gender as the subject being replaced.

For intra-subject CV for BD exceeding the assumed 30% in Part 2, the sample size of 48 subjects per treatment group could be increased up to a maximum of 50 subjects per treatment group.

Analysis:

Pharmacokinetic and Bleeding

Part 1: Intra-subject CV for BD and BV were estimated using mixed-effect modeling of the data. Based on the results of Part 1 (Protocol Amendment 2), an intra-subject CV for BD was estimated to be 25% and for BV was estimated to be 57%.

Part 2: For each endpoint (BD and BV), a mixed-effect model that included time as a fixed effect, and subject as a random effect was used to estimate the least squares means and intra-subject CV. The point estimates and 95% CIs for the difference in means of BD and BV on a log scale between posttreatment and baseline were constructed. The limits of the CIs were retransformed using antilogarithms to obtain 95% CIs for the ratios of the mean values for the posttreatment over baseline (posttreatment/baseline) for each treatment group.

The comparisons of interest for between treatment groups were as follows:

- Treatment Group A vs Treatment Group C
- Treatment Group B vs Treatment Group C

For each bleeding parameter (BD and BV), a mixed effect model was fitted to the log transformed change from baseline bleeding parameter data as the dependent variable, and treatment group, as a fixed effect and subject as a random effect. Using these estimated least square means and estimated inter-subject variance, the point estimate and 95% CIs for the difference in means on a log scale between test and reference were constructed for each comparison of interest.

The limits of the CIs were retransformed using antilogarithms to obtain 95% CIs for the ratios of the mean values for bleeding parameters of the test to reference for each comparison of interest.

Descriptive statistics of BD, BV, PT, and TGA values and change from baseline were summarized by treatment group.

Bar charts with the upper limit of 95% CI error bars were generated for each treatment group for the mean ratio of posttreatment to baseline in the same graph from BD, BV, TGA, and for mean percent change from baseline in PT.

Mean line plots with upper limit of 95% CI error bars were generated for the each treatment group for PT and TGA percent change from baseline vs time in the same graph.

Pharmacokinetic

Descriptive statistics were used to summarize the rivaroxaban plasma concentration data and PK parameters for all subjects as a single group (Part 1) and as individual treatment groups (Part 2).

In Part 2, the C_{trough} values of rivaroxaban were tabulated and visually inspected for steady state. Individual, composite, and mean concentration vs time profiles were plotted by treatment group using both linear and semi-logarithmic scale.

Pharmacodynamic

Descriptive statistics were used to summarize the PD parameters (PT and TGA) for all subjects as a single group (Part 1) and by individual treatment groups (Part 2) at each measured timepoint. Mean profiles for each of the PD parameters vs time were plotted. The absolute and percentage change from baseline (Day 4, 3 hours) in the PD parameters at each measured timepoint were summarized using mean, standard deviation (SD), and 95% CIs.

Exploratory Biomarkers

No biomarker assessments were collected in Part 1.

In Part 2, descriptive statistics were presented for each treatment group at each measured timepoint. Mean profiles for each biomarker versus time were plotted. The absolute values at each measured timepoint were summarized using mean, SD, and 95% CIs for all biomarkers.

Safety Analyses

Safety was evaluated by examining the incidence and type of AEs, and changes in clinical laboratory test values, physical examination results and vital signs measurements. All subjects who received at least 1 dose of the rivaroxaban were included in the safety and tolerability analysis. Baseline for all laboratory evaluations was taken at the Screening Visit and for vital signs as the last evaluation done before the rivaroxaban administration of each Part of the study. For each AE, the percentages of subjects who experienced at least 1 occurrence of the given event were summarized by treatment group. Descriptive statistics were calculated for each laboratory analyte and vital signs values and changes from baseline at each measured timepoint were summarized. Physical examination results were listed.

RESULTS:

STUDY POPULATION:

A total of 12 subjects were enrolled in Part 1 (rivaroxaban monotherapy) of the study. A total of 147 subjects were enrolled in Part 2 of the study, 49 subjects each in Treatment Group A (rivaroxaban 20 mg + Kcentra), B (rivaroxaban 20 mg + TXA), and C (rivaroxaban 20 mg + saline placebo). Of the

total 147 subjects, 145 (98.6%) subjects completed the study, one subject each in Treatment Group A and Treatment Group B withdrew consent from the study.

All 12 subjects were men in Part 1 of the study. The median (range) age of subjects was 29.5 years (19 to 55 years) and the mean (SD) BMI was 26.3 (2.9) kg/m^2. There were more men (103 [70.1%]) compared to women (44 [29.9%]) in Part 2 of the study. Most of the subjects were white (97 [66.0%]) by race. The median (range) age of subjects was 28.0 years (18 to 54 years) and the mean (SD) BMI was 25.0 (3.1) kg/m^2. Five major protocol deviations were reported in Part 2 of the study.

BLEEDING PARAMETERS - PUNCH BIOPSY:

Part 1:

Bleeding Duration and Bleeding Volume:

At baseline (Day -1), mean (SD) BD was 9.36 (2.36) minutes (range 5.2 to 12.7 minutes), which was slightly above the normal range (2 to 9 minutes). Following a single 20-mg dose of rivaroxaban, there was an approximate doubling in the BD compared with baseline BD values, with a geometric least-square (LS) mean ratio of 201.4 (95% CI: 161.92 to 250.51).

The mean (SD) BV at baseline (Day -1) was approximately 2.23 (0.985) mL. Following 20-mg dose of rivaroxaban, BV increased to approximately 4.41 (2.881) mL, which was less than a doubling in volume compared with the baseline values with a geometric LS mean ratio of 182.5 (95% CI: 113.47 to 293.56).

Part 2:

Bleeding Duration and Bleeding Volume:

At baseline (Day -1), the mean (SD) BD for subjects in Treatment Groups A (4-Factor PCC / Kcentra), B (Tranexamic Acid / TXA), and C (Saline control), respectively, were 9.95 (2.95), 9.85 (3.03), and 9.30 (3.20) minutes with the corresponding mean (SD) BV values of 2.67 (2.29) mL, 2.53 (1.84) mL, and 3.39 (4.96) mL. The mean (SD) values for BD measured on Day 4 following the administration of rivaroxaban 20-mg twice-daily to steady-state were 17.71 (5.81), 17.84 (6.01), and 17.56 (6.10) minutes with the corresponding BV of 4.05 (2.88), 4.53 (3.15), and 4.28 (2.64) mL after Treatments A, B, and C, respectively.

For each treatment group, there was slightly less than a doubling in the mean BD for all treatment groups. The results of the BV changes were generally consistent with the results observed in the BD for all 3 treatment groups.

When compared with the saline control (Treatment C), there were no considerable differences in either the baseline adjusted BD or the baseline adjusted BV after receiving 4-Factor PCC, Kcentra (50 IU/kg → TXA saline control in Treatments Group A) and Tranexamic acid (Kcentra saline control → TXA in Treatment Group B). For baseline adjusted BD, the geometric LS mean ratio was 92.7 (95% CI: 78.31 - 109.78; p-value 0.3779) for the Kcentra and 94.1 (95% CI: 79.45 - 111.37; p-value 0.4751) for the TXA Treatment Group, when compared with the saline control group. For baseline adjusted BV, the geometric LS mean ratio was 95.3 (95% CI: 66.16 - 137.16; p-value 0.7926) for the Kcentra Treatment Group and 108.9 (95% CI: 75.66 - 156.86; p-value 0.6431) for the TXA Treatment Group when compared with the saline control group.

PHARMACODYNAMIC RESULTS:

The absolute values of the various PD markers have been presented within the results section. The change from baseline and percent change from baseline results followed the same trend as the absolute value results and is summarized within the supporting PD Attachments.

Part 1:

Prothrombin Time

Following the administration of a single 20-mg dose of rivaroxaban, there was a mean increase from baseline in PT of approximately 6.5 seconds, reaching a maximum mean absolute PT prolongation of approximately 20 seconds at 4 hours postdose. Subsequently, there was a reduction in the mean absolute PT value as it reverted to baseline values at 24 hours postdose.

Thrombin Generation Assay

The data derived from the automated TGA was used to determine the ETP; which is represented as the AUC, the Time to Peak (TP), and the Lag Time (LT) that is generated from the assay.

Endogenous Thrombin Potential

Following the administration of a single 20-mg dose of rivaroxaban, the ETP (measured by the changes in AUC of the thrombin generation curve) decreased. The mean (SD) ETP value was 82.07 (10.19) at baseline (Day 1, predose) with a maximum mean decrease to 57.01 (14.52) nmol/L*s at 3 hours postdose. Mean ETP values reverted towards baseline values eventually surpassing the baseline (Day -1) levels between 10 and 12 hours postdose, with slight increases occurring until 14 hours and then plateaus until 24 hours (the last measurement).

Time to Peak

The administration of a single 20-mg dose of rivaroxaban prolonged the time required to reach peak (TP) thrombin levels. The mean absolute TP for thrombin levels was eventually obtained around 3 to 4 hours postdose, after which the thrombin levels showed only minor fluctuations until 5 hours postdose. At 24 hours postdose, the TP decreased and eventually surpassed the baseline (Day -1) value.

Lag Time

The administration of a single 20-mg dose of rivaroxaban prolonged the time required before thrombin is generated (LT) by approximately 12 to 13 minutes. The LT fluctuated for the next 1 hour from its onset until 5 hours postdose where the values began to decline gradually. At 24 hours postdose, the LT was similar to the pre-study baseline level.

Part 2:

Prothrombin Time

Following the administration of rivaroxaban 20 mg twice daily, mean trough PT values at steady-state for subjects in all 3 Treatment Groups were approximately 18 seconds. This represents an approximate 4.5 second increase from mean pre-study baseline (Day -1) values (13.5 seconds). After the final administration of rivaroxaban 20 mg on the morning of Day 4, the maximum mean PT value increased to approximately 25 seconds for all 3 Treatment Groups. Within 15 minutes of the administration of Kcentra (Treatment Group A), there was a reduction of mean PT values by approximately 4 seconds, after which the mean values remained lower in comparison to the saline control (Treatment Group C) until approximately 48 hours postdose. In comparison, after the administration of TXA (Treatment Group B) the mean PT values mirrored those observed with the saline control (Treatment Group C). By 48 hours postdose, all 3 treatment groups displayed similar values that were consistent to the respective mean predose baseline values in each treatment group.

Thrombin Generation Assay

Endogenous Thrombin Potential

Following the administration of rivaroxaban 20 mg twice daily, with the final dose on the morning of Day 4, ETP values (measured by changes in AUC of the thrombin generation curve) decreased in all 3 treatment groups. Following the administration of Kcentra (Treatment Group A), the ETP values rapidly increased in comparison with the saline control (Treatment Group C) surpassing the mean baseline (Day -1) value within 30 minutes postdose. The ETP values continued to increase steadily until approximately 24 hours postdose, at which time the values began to decrease towards the predose baseline values for up to 168 hours postdose. Following the administration of TXA (Treatment Group B), the ETP values continued to increase gradually but at a slightly lower rate than the saline control (Treatment Group C). The ETP values reached the predose baseline value at approximately 48 hours postdose, and remained at that level.

Time to Peak

Following the administration of rivaroxaban 20 mg twice daily to steady-state, the TP for thrombin levels following the final administration of rivaroxaban on the morning of Day 4 was prolonged in all treatment groups. Following the administration of Kcentra (Treatment Group A), the TP began to decline rapidly in comparison with the saline control (Treatment Group C). Following the administration of TXA (Treatment Group B), a slight decline in TP was observed only after 15 minutes post TXA administration. Time to Peak continued to decline and mirrored the changes observed with the saline control (Treatment Group C) for the subsequent timepoints. By 48-hour postdose, the TP values were similar for all 3 treatment groups and reached the pre-study baseline value (Day -1) after 72 hours.

Lag Time

Following the administration of rivaroxaban 20 mg twice daily to steady-state, with the final dose occurring on the morning of Day 4, the time required before thrombin is generated (or LT) was prolonged by approximately 5 to 8 minutes in all 3 treatment groups. After this initial prolongation in the LT that occurred within the first 2 hours postdose and prior to receiving any of the treatments, the LT began to gradually decrease in Treatment Group A, fluctuated in Treatment Group B, and remained steady in Treatment Group C. Following the administration of Kcentra (Treatment Group A), the LT steadily declined and was much lower in comparison to saline control (Treatment Group C). Following the administration of TXA (Treatment Group B), the LT declined gradually and was similar to the values observed after administration of the saline control. By 24 hours postdose, the LT values remained prolonged for all treatments in comparison to their respective predose baseline (Day -1) values, which continued to 72 hours postdose.

PHARMACOKINETIC RESULTS:

Part 1:

The PK parameters derived after a single 20-mg dose of rivaroxaban were consistent with the results observed in earlier studies that assessed the same dose regimen.

Part 2:

Through the assessment of mean trough plasma concentration values, it appeared that rivaroxaban reached steady-state concentration by Day 3 of the study. The mean steady-state plasma concentration-time profiles of rivaroxaban after oral administration of a 20-mg twice-daily dose regimen were consistent with data obtained from previous clinical pharmacology studies that assessed the same regimen.

In general, mean steady-state rivaroxaban plasma PK parameters were similar across the 3 treatment groups and were consistent with the results observed in earlier studies that assessed the 20-mg twice-daily dose regimen.

EXPLORATORY BIOMARKERS:

Part 1:

No exploratory biomarker assessments were collected in Part 1.

Part 2:

Blood and plasma samples were analyzed to determine the exploratory biomarkers proteins FII, FVII, FIX, FX, Protein C, Protein S, F1+2, D-Dimer, and TAT using validated methods.

D-dimer

Changes in the D-dimer levels were reviewed to assess the potential for thromboembolic events. Overall, the D-dimer concentrations remained unchanged in all subjects across the 3 Treatment Groups. The D-dimer levels were observed as being either close to or more or less than the pre-study baseline (Day 4 predose) values for all the sampling timepoints.

Prothrombin Fragment 1+2

Changes in F1+2 concentrations were reviewed to assess the development of a hypercoagulable state. Following the administration of Kcentra (Treatment Group A), a sudden increase in F1+2 levels was observed. These values rapidly returned towards pre-study baseline (Day 4 predose) by 24 hours postdose. In comparison, the administration of TXA (Treatment Group B) and saline control (Treatment Group C) had no appreciable effects on F1+2 levels.

Thrombin-Antithrombin Complex

Following the administration of Kcentra (Treatment Group A), TAT levels increased to approximately 12 μg/L and gradually declined back to pre-study baseline (Day 4 predose) values by 72 hours postdose. In comparison, TAT levels following the administration of TXA (Treatment Group B) increased slightly at 24 hours postdose and returned to predose baseline values by 72 hours. A similar trend in TAT increase was observed with the saline control (Treatment Group C).

Coagulation Factors II, VII, IX, X and Proteins C and S

Following the administration of Kcentra (Treatment Group A), there was a steep decrease observed at the first sampling timepoint (24 hours postdose) for Factors II and X along with decreases in Proteins C and S. Factors VII and IX displayed a relatively smaller increase at 24 hours postdose. Neither the

administration of TXA (Treatment Group B) nor the saline control (Treatment Group C) appeared to have any influence on these factors and proteins.

SAFETY RESULTS:

All subjects who received at least 1 dose of the study agent were included in the safety and tolerability analysis.

Part 1: The overall incidence of treatment emergent adverse events (TEAEs) was low (3 [25.0%] subjects). The reported TEAEs were post procedural hemorrhage (1 event), which was considered mild and very likely related to rivaroxaban, and upper respiratory infection (2 events), which were considered mild and not related to rivaroxaban.

Part 2: Overall, 62 (42.2%) of 147 subjects were reported with TEAEs during Part 2; 21 (42.9%) subjects in Treatment Group A, 24 (49.0%) subjects in Treatment Group B, and 17 (34.7%) subjects in Treatment Group C. As per the system organ class (SOCs), the incidence of TEAEs was higher (>10%) in gastrointestinal disorders (28/147 [19.0%]) and nervous system disorders (28/147 [19.0%]). By preferred term, the most commonly reported TEAEs (≥10 subjects) were nausea (n=19, 12.9%), headache (n=16, 10.9%), and dizziness (n=10, 6.8%).

The majority of TEAEs were mild in intensity except for the TEAEs of nausea (n=1) and menorrhagia (n=2), which were moderate in intensity. The majority of the TEAEs were considered by the investigator to be either not related or doubtfully related to the study treatment.

The events that were considered by the investigator to be very likely related to the study treatment were: nausea (n=11), gingival bleeding and dizziness (n=4 each), menorrhagia (n=3), incision site hemorrhage, epistaxis, hyperhidrosis and chromatopsia (n=2 each), incision site hematoma, subcutaneous hematoma, ecchymosis, visual impairment, and hematoma (n=1 each).

No deaths or serious adverse events (SAEs) were reported in this study. None of the subjects withdrew from the study due to AEs. A total of 13 subjects were reported with AEs of clinical interest: post procedural hemorrhage, gingival bleeding incision site hematoma, incision site hemorrhage, hematoma, subcutaneous hematoma, and menorrhagia.

No clinically relevant laboratory changes, vital signs abnormalities, physical examination abnormalities, or ECG abnormalities were reported during the study.

STUDY LIMITATIONS:

A potential study limitation is the use of a supratherapeutic 20-mg twice-daily dose regimen. This regimen, which was used in the Eerenberg and Levi studies and covered some of the potential exposure increases observed in subjects with renal impairment and older age, produced plasma concentrations of rivaroxaban that were higher than what is achieved with the currently approved 20-mg once-daily dose. In selecting this regimen, perhaps the punch biopsy model was not sensitive enough to show a reversal at this higher concentration. Perhaps the approved dosage regimen should be assessed in the future.

CONCLUSIONS:

- No reversal of punch biopsy bleeding parameters (BD or BV) was observed with either Kcentra (Treatment Group A) or TXA (Treatment Group B).
- Kcentra (Treatment Group A) partially reversed the rivaroxaban-induced prolongations in PT. These results were consistent with those observed in the previous PCC study (RIVAROXNAP1003).
- Tranexamic Acid (Treatment Group B) did not appear to reverse the rivaroxaban-induced prolongations in PT.

- Kcentra (Treatment Group A) appeared to fully reverse the rivaroxaban-induced changes in ETP and partially reverse the TP and LT parameters of the TGA. These results were consistent to those observed in the previous PCC study (RIVAROXNAP1003).
- Tranexamic Acid (Treatment Group B) did not appear to reverse the rivaroxaban-induced changes in ETP or the other parameters of the TGA.
- Neither Kcentra (Treatment Group A) nor TXA (Treatment Group B) affected the PK properties of rivaroxaban.
- D-dimer was not affected by the Kcentra (Treatment Group A) or TXA (Treatment Group B) treatments. Prothrombin factor 1+2 was initially elevated after Kcentra administration and returned to predose baseline levels by 24 hours postdose, while TXA had no effect. Thrombin-antithrombin complex levels were elevated following Kcentra treatment and returned to predose baseline levels by 72 hours postdose. While TAT levels did increase around 24 hours postdose following TXA administration and returned to predose baseline levels by 72 hours postdose, these marginal increases followed the same trend as the saline control (Treatment Group C).
- Following the administration of Kcentra (Treatment Group A), there was a steep increase observed at the first sampling timepoint (24 hours postdose) for Factors II and X along with increases in Proteins C and S. Factors VII and IX displayed a much smaller increase at 24 hours postdose. Neither the administration of TXA (Treatment Group B) nor the saline control (Treatment Group C) appeared to have any influence on these factors and proteins.
- Following the administration of rivaroxaban 20 mg, the AEs observed in this study were consistent with the known safety profile of rivaroxaban (Xarelto) and no new safety signals were identified.
- Co-administration of rivaroxaban 20 mg with Kcentra (50 IU/kg), TXA (1.0 g), or saline appeared to be safe and well tolerated, and no serious bleeding or thrombotic AEs were identified.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.