SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	To be determined
Name of Active Ingredient(s)	JNJ-39039039 BAY 59-7939 (Rivaroxaban)

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Status: Approved
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Prepared by: Janssen Research & Development, LLC

Protocol No.: RIVAROXCRF1001

Title of Study: An Open-label Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of a Single Dose of Rivaroxaban in Subjects with End-Stage Renal Disease (ESRD) on Maintenance Hemodialysis

NCT No.: NCT02289703

Clinical Registry No.: CR105711

Coordinating Principal Investigator: [redacted], MD, [redacted], United States

Study Center: [redacted], United States

Publication (Reference): None

Study Period: 09 January 2015 to 30 March 2015

Phase of Development: 1

Objectives:

Primary objectives of the study were:

- To characterize the single-dose pharmacokinetics (PK) of rivaroxaban (administered as a single 15-mg dose, once before and once after dialysis) in subjects with end-stage renal disease (ESRD) who are on maintenance hemodialysis.
- To compare the PK of single 15-mg doses of rivaroxaban given before and after dialysis in subjects with ESRD to the PK in healthy control subjects (matched with respect to sex, age and body mass index [BMI]) with creatinine clearance (CL_{CR}) ≥80 mL/min.

Secondary objectives of the study were:

- To assess the fraction of a predialysis rivaroxaban dose that is removed by hemodialysis.
- To assess the single-dose pharmacodynamics (PD) of rivaroxaban (administered as a single 15-mg dose, once before and once after dialysis) in subjects with ESRD.

- To assess safety and tolerability of rivaroxaban in subjects with ESRD.

Methodology:

This was an open-label, single-dose, single-center, parallel-group study to characterize the PK, PD, and safety of a single 15-mg dose of rivaroxaban in both clinically stable subjects with ESRD on maintenance hemodialysis and in healthy control subjects with a CL_{CR} ≥80 mL/min.

The study consisted of 2 study groups - Group A consisted of subjects with ESRD requiring hemodialysis for at least 3 months before screening and Group B consisted of healthy control subjects group-matched to Group A for age, sex, and BMI with CL_{CR} ≥80 mL/min and no evidence of kidney damage.

The study consisted of a screening phase (within 21 days prior to admission into the study center on Day 1), followed by 2 treatment periods for ESRD subjects (Group A), or 1 treatment period for healthy control subjects (Group B). All subjects were confined to the study center for the duration of each treatment period.

Group A (ESRD subjects) - During Treatment Period 1, subjects received a single 15-mg oral dose of rivaroxaban, 2 (±0.5) hours before the start of a 4-hour hemodialysis session which was followed by a 7- to 14-day washout period. On returning to the study center for Treatment Period 2, subjects received a single 15-mg oral rivaroxaban dose, 3 hours after the completion of a 4-hour hemodialysis session. Pre- and postdialysis PK and PD samples were taken at various individual timepoints on Days 1 through 4 during both treatment periods.

Group B (healthy control subjects) - Treatment consisted of a single period (Period 1) during which the subjects received a single 15-mg oral dose of rivaroxaban with pre- and postdose PK and PD samples taken at various individual timepoints on Days 1 through 4. Subjects in Group B were not enrolled until all subjects in Group A had been identified and all demographic information was available.

For all subjects, the 15-mg dose of rivaroxaban was administered 30 minutes after the start of a standardized meal.

Healthy control subjects in Group B were matched to the ESRD subjects in Group A with respect to sex (same proportion in each population), mean age (±10 years) and BMI (±20%). All ESRD subjects (Group A) were in stable physical condition, consistent with ESRD, free of concomitant clinically significant hepatic or cardiac disease, requiring two or three 4-hour hemodialysis sessions per week. These dialysis sessions were performed under a "tight heparinization" schedule using unfractionated heparin (UFH), ie, initial intravenous (IV) bolus of 500 units of UFH prior to the start of dialysis followed by an infusion of 500 U/h for 3 hours, at which time the infusion was terminated (total dose of 2000 U UFH). Additional heparin use during dialysis was allowed if the investigator deemed it appropriate.

Any subject who prematurely withdrew from the study before the collection of 72-hour PK and PD samples (end of Period 2 for Group A and end of Period 1 for Group B) was required to complete all end-of-study procedures before discharge from the study site.

Number of Subjects (planned and analyzed):

Planned: Approximately 16 subjects were to be enrolled - 8 subjects with clinically stable ESRD and on maintenance hemodialysis and 8 healthy control subjects with a CL_{CR} ≥80 mL/min.

Analyzed: A total of 16 subjects were analyzed and included in safety, PK, and PD analysis. All 16 subjects completed the study.

Diagnosis and Main Criteria for Inclusion: Men and women ≥18 years of age; BMI between 18 and 38 kg/m², inclusive; a body weight of not less than 50 kg, and characterized either as having ESRD requiring dialysis or, for healthy control subjects, having CL_{CR} ≥80 mL/min.

Subjects receiving hemodialysis must have been in stable physical condition consistent with ESRD, free of concomitant clinically significant hepatic or cardiac disease and have been receiving hemodialysis 2 or 3 times a week for at least 3 months prior to screening and were judged suitable to receive "tight heparinization" during a standard 4-hour hemodialysis session.

Test Product, Dose and Mode of Administration, Batch No.: Rivaroxaban tablets, 15-mg single oral dose administration (Lot No.: 4370281; Expiry date: Oct 2016)

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable

Duration of Treatment: For subjects in Group A (ESRD subjects), each treatment period had a duration of 4 days (Day -1 to 72 hours postdose on Day 4) separated by a washout period of 7 to 14 days. The total study duration for ESRD subjects was approximately 43 days. The total study duration for healthy matched control subjects was approximately 25 days (assuming a 21-day screening period and one 4-day treatment period).

Criteria for Evaluation:

Pharmacokinetic: Serial blood samples were collected from each subject prior to and for 72 hours following the administration of rivaroxaban for the measurement of rivaroxaban plasma concentrations during Treatment Periods 1 and 2 for Group A and during Treatment Period 1 for Group B. On Day 1 of Period 1, a 6-mL venous blood sample was drawn from subjects in both groups together with the predose PK blood sample for the determination of the fraction unbound (f_u) of rivaroxaban. An additional postdialysis blood sample was drawn for f_u immediately upon completion of the dialysis procedure from subjects in Group A at the time of 6-hour PK sample. Rivaroxaban concentrations were also measured in urine from ESRD subjects in Group A who could produce urine, and from all subjects in Group B, and in dialyzer plasma and dialysate fluid (Group A only).

From the plasma, urine, and dialysate data the following key noncompartmental PK parameters were determined for each group: f_u, C_{max}, t_{max}, AUC_{last}, AUC_{∞}, CL/F, Vd_z/F, $t_{1/2,\lambda}$, Ae_{urine}, $Ae_{,\%dose}$, CL_R, CL_{NR} (calculated as $CL/F - CL_R$), CL_{CR} (Cockcroft-Gault estimate from mean serum creatinine), CL_{GFR} (calculated as $f_u \times CL_{CR}$), CL_{ACT} (calculated as $CL_R - CL_{GFR}$), CL_{ACT}/CL_R, and $CL_{ACT}/(CL/F)$. Based on the individual dialysate data for subjects in Group A, the concentration of rivaroxaban in dialyzer plasma and dialysate fluid was determined at each timepoint. From these data, hemodialyzer extraction ratio of the drug (ER), hemodialysis clearance (CL_D), and percentage of the administered dose recovered in the dialysate fluid (%DIAL) were calculated.

Pharmacodynamic: Pharmacodynamic evaluations were based upon serial Neoplastin Plus® PT, FXa inhibition, and anti-FXa activity. The PD measurements were obtained for each subject in Group A during both treatment periods and Group B during Treatment Period 1 prior to and for up to 72 hours following the administration of rivaroxaban. The following key PD parameters (using absolute, change from baseline, and percent change), for each of the PD markers was calculated by treatment period for each subject group: $AUCEC_{72}$ and E_{max}.

Pharmacogenomics (DNA): A pharmacogenomic blood sample (10 mL) was collected on Day -1 to allow for future pharmacogenomic research.

Safety: Safety and tolerability were evaluated throughout the study and included the collection of adverse events (AEs) subject's physical examination (including height and body weight), vital signs (blood pressures, pulse rate, and body temperature), 12-lead electrocardiograms (ECGs) and safety laboratory tests (including hematology, coagulation profile, serum chemistry, and urinalysis)

Residual Renal Function: Renal function (as defined by CL_{CR} value) was not formally assessed for all subjects in Group A. However, in order to assess any residual renal function, subjects in Group A were classified as "anuric"(<50 mL/day), "oligo-anuric" (50-250 mL/day), or not oligo-anuric (>250 mL/day)

based on urine volume collected during the 24 hour interval on Day 1. Serum creatinine was assessed for subjects who produced ≥50 mL of urine and CL_{CR} was calculated.

For subjects in Group B, renal function was assessed by the CL_{CR} values (Cockcroft-Gault equation) based on 2 separate measurements, 7 days apart, within the screening period.

Statistical Methods:

Sample Size Determination: Based on the results of RIVAROXACS1001 study, the estimated intersubject coefficients of variation (CV) for PK parameters (AUCs and C_{max}) ranged from 27% to 29%, and the estimated intersubject CV for PD parameters ($AUCEC_{72}$ and E_{max} for prothrombin time [PT], FXa inhibition and anti-FXa) ranged from 27% to 43% for rivaroxaban in subjects with mild or moderate renal impairment and in subjects with normal renal function. Assuming the inter-subject CV are the same as the maximum estimated CV of 29% for PK parameters and 43% for PD parameters for rivaroxaban, a sample size of 8 subjects who complete each treatment period in the ESRD group and 8 completed healthy matched control subjects with CL_{CR} ≥80 mL/min would be sufficient for the point estimates of the ratio of mean PK and PD parameters of each treatment period (Period 1, Period 2) in the ESRD group vs. the healthy matched control subjects with CL_{CR} ≥80 mL/min to fall within 77.4% to 129.0% and 68.4 to 146.0%, respectively, of their true values with 90% confidence.

Based on the results from study RIVAROXACS1001, the estimated intrasubject CV for the PK parameters (AUCs and C_{max}) ranged from 14% to 16% and the estimated intrasubject CV for the PD parameters (AUC and E_{max} for PT, FXa inhibition and anti-FXa) ranged from 37% to 41% for rivaroxaban in subjects with normal renal function, and mild or moderate renal impairment. Assuming the intrasubject CV are the same as the maximum estimated CV of 16% for the PK parameters and 41% for the PD parameters for rivaroxaban, a sample size of 8 subjects who complete all of the treatment periods in the ESRD group would be sufficient for the point estimates of the ratio of mean PK and PD parameters of rivaroxaban, following single-dose administration of a 15-mg dose of rivaroxaban 2 (±0.5) hours before the start of a 4-hour hemodialysis session (Treatment Period 1) vs. 3 hours after completion of a 4-hour hemodialysis session (Treatment Period 2) to fall within 85.8% to 116.6%, and 67.8% to 147.6%, respectively, of its true values with 90% confidence.

Pharmacokinetics Assessments: Based on the rivaroxaban plasma, dialysate, and urine concentration data, the following statistics were calculated for each of the sampling points, by treatment and for ESRD and control subjects groups separately: arithmetic mean, standard deviation (SD) and CV, geometric mean, minimum, median, maximum value and the number of measurements.

Individual, composite and mean concentration vs. time profiles was plotted by treatment and study population using both linear and semi-logarithmic scale. Pharmacokinetic parameters were summarized by descriptive statistics.

The primary parameters of interest for the statistical analysis were the log-transformed estimated AUCs (AUC_{∞}, AUC_{last}) and C_{max}.

For each log-transformed PK parameter, a mixed effects model was used to estimate the least squares means (LSM) and inter-subject variance; the model included renal function group as a fixed effect and subject as a random effect. Using the estimated LSMs and intersubject variance, the point estimate and 90% confidence intervals (CI) for the difference in means on a log scale was constructed. The limits of the CIs were retransformed using antilogarithms to obtain 90% CIs for the ratios of the geometric mean PK parameters of the test (Group A [ESRD subjects] Period 1, Group A [ESRD subjects] Period 2) to reference Group B (healthy matched control subjects) Period 1.

Only the data from subjects who completed all of the treatment periods in the ESRD group were included in the between treatment periods PK parameter comparisons. If one of the PK parameters of interest is not

estimable for a given subject in 1 period, the subject's data were not to be included in the statistical analysis of that particular PK parameter.

For each log-transformed PK parameter, a mixed effect model was used to estimate the LSMs and intrasubject variance; the model included treatment period as a fixed effect and subject as a random effect. Using the estimated LSMs and intrasubject variance, the point estimate and 90% CIs for the difference in means on a log scale was constructed. The limits of the CIs were retransformed using antilogarithms to obtain 90% CIs for the ratios of the mean AUCs and C_{max} of the test (Group A [ESRD subjects] Period 1) to reference (Group A [ESRD subjects] Period 2).

Pharmacodynamic Assessments: Pharmacodynamic assessments included descriptive statistics, including arithmetic mean, SD, CV, median, minimum and maximum were calculated by treatment and study population at each sampling time. Absolute, change from baseline, and percent change from baseline in PD measurements were also summarized by arithmetic mean, SD, CV, median, minimum and maximum at each postdose timepoint.

The primary parameter of interest for the statistical analysis was log-transformed estimated PD parameters (AUC and E_{max} for PT and FXa inhibition PD markers of absolute, change from baseline, and percent change values and for absolute values of anti-FXa).

For each log-transformed PD parameter, a mixed effects model was used to estimate the LSMs and intersubject variance; the model includes renal function group as a fixed effect and subject as a random effect. Using the estimated LSMs and intersubject variance, the point estimate and 90% CIs for the difference in means on a log scale will be constructed. The limits of the CIs were retransformed using antilogarithms to obtain 90% CIs for the ratios of the mean AUC and E_{max} of the test to reference condition. Comparisons of interest are identical to same made above in pharmacokinetics.

Only the data from subjects who complete all the treatment periods in the ESRD group were included in the between treatment periods PD parameter comparisons. If 1 of the PD parameters of interest is not estimable for a given subject in 1 treatment period, the subject's data was not included in the statistical analysis of that particular PD parameter.

For each log-transformed PD parameter, a mixed effects model was used to estimate the LSMs and intrasubject variance; the model included treatment period as a fixed effect and subject as a random effect. Using the estimated LSMs and intrasubject variance, the point estimate and 90% CIs for the difference in means on a log scale was to be constructed. The limits of the CIs were retransformed using antilogarithms to obtain 90% CIs for the ratios of the mean PD parameters (AUCs and E_{max}) of the test (Group A [ESRD subjects] Period 1) to reference (Group A [ESRD subjects] Period 2).

Pharmacogenomics: A 10-mL blood sample was collected from all enrolled subjects and stored for future research. No pharmacogenomic analyses were performed for this study.

Safety Assessments: All subjects who were assigned to treatment and received at least a partial dose of the study agent (rivaroxaban) were included in the safety and tolerability analysis. Safety was evaluated by examining the incidence and types of AEs, changes in clinical laboratory test values (blood chemistry, hematology, coagulation tests, ie, PT and activated partial thromboplastin time [aPTT] and urinalysis), physical examination, 12-lead ECG, and vital sign results from the screening phase through study completion, including the washout intervals.

RESULTS:

STUDY POPULATION:

A total of 16 subjects were enrolled and assigned to individual treatment groups. Eight subjects with ESRD on maintenance hemodialysis were assigned to Group A (Periods 1 and 2) and 8 healthy control subjects (CL_{CR} ≥80 mL/min) were assigned to Group B, respectively.

Overall, the demographic and baseline characteristics of all study subjects, assigned to individual treatment groups were consistent with protocol inclusion and exclusion criteria. All subjects were men and majority were white (63%). The mean (SD) age of the subjects in Group A was 46.4 (12.91) years and in Group B was 49.3 (6.52) years, respectively. The mean BMI for subjects in Group A was 31.5 kg/m^2 and ranged from 22.0 to 38.0 kg/m^2. The mean BMI for subjects in Group B was 30.0 kg/m^2 and ranged from 27.0 to 33.0 kg/m^2. The mean CL_{CR} for subjects in Group B ranged from 100.9 mL/min to 175.2 mL/min which was well above the desired ≥80 mL/min. Of the 8 subjects in Group A, 3 subjects had measured CL_{CR} of 0, 2, and 6 mL/min, respectively.

There were no major protocol deviations in this study that impacted the subject's rights, safety, or well-being or the completeness, accuracy, and reliability of the study data.

PHARMACOKINETIC RESULTS:

Rivaroxaban was rapidly absorbed. Average peak plasma levels were highest for the ESRD subjects dosed 3 hours after (postdialysis) undergoing a 4-hour hemodialysis session. In ESRD subjects that received the dose 2 hours prior to dialysis (predialysis), the average peak plasma levels were similar to subjects with normal renal function.

Geometric mean C_{max} decreased by approximately 9%, while geometric mean AUC_{∞} and AUC_{last} values increased approximately 48% for ESRD subjects dosed 2 hours before (predialysis) undergoing a 4-hour hemodialysis session when compared to the normal renal function group. Geometric mean C_{max} increased by approximately 18% and geometric mean AUC_{∞} and AUC_{last} values increased approximately 56% for ESRD subjects dosed 3 hours after (postdialysis) undergoing a 4-hour hemodialysis session when compared to the normal renal function group.

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Rivaroxaban Pharmacokinetic Parameters (ESRD vs. Normal Renal Function)

	Parameter	N	Geometric Mean ESRD (Test)	Geometric Mean Normal Renal Function (Reference)	Geometric Mean Ratio (90% CI)
Predialysis	C_{max} (ng/mL)	8	188.91	208.03	90.81 (77.47 - 106.44)
	AUC_{last} (ng.h/mL)	8	2,675.86	1,812.99	147.59 (122.72 – 177.5)
	AUC_{∞} (ng.h/mL)	8	2,704.55	1,839.68[a]	147.01 (120.6 – 179.21)
Postdialysis	C_{max} (ng/mL)	8	244.91	208.03	117.73 (100.44 - 137.99)
	AUC_{last} (ng.h/mL)	8	2,814.07	1,812.99	155.22 (129.06 – 186.67)
	AUC_{∞} (ng.h/mL)	8	2,862.10	1839.68[a]	155.58 (127.63 – 189.64)

[a] N=7; healthy Subject [redacted] was excluded from $AUC_{(0-\infty)}$ PK parameter analysis due to variability in the terminal phase (r^2adj.<0.9000)

Note: Analysis done on log-transformed data and the results were back-transformed using anti-logarithms
Test - Group A (Period 1): ESRD subjects (15-mg rivaroxaban administered 2 (±0.5) hours before HD session)
Test - Group A (Period 2): ESRD subjects (15-mg rivaroxaban administered 3 hours after HD session)
Reference - Group B: Healthy matched control subjects ($CL_{CR} \geq 80$ mL/min) (15-mg dose of rivaroxaban administered 30 minutes after the start of meal)
CI= confidence interval, CL_{CR}= creatinine clearance; ESRD=end-stage renal disease, HD=hemodialysis

Additionally, geometric mean C_{max} and AUC values were approximately 23% and 5.5% lower, respectively in the predialysis group compared to the postdialysis group.

Statistical Analyses Results: Geometric Means and the Ratio of Geometric Means With Corresponding 90% Confidence Intervals for Rivaroxaban Pharmacokinetic Parameters (ESRD Predialysis vs. ESRD Postdialysis)

Parameter	N	Geometric Mean Predialysis (Test)	Geometric Mean Postdialysis (Reference)	Geometric Mean Ratio (90% CI)
C_{max} (ng/mL)	8	188.91	244.91	77.13 (64.17 – 92.72)
AUC_{last} (ng.h/mL)	8	2,675.86	2,814.07	95.09 (84.98 – 106.39)
AUC_{∞} (ng.h/mL)	8	2,704.55	2,862.10	94.50 (84.16 – 106.1)

Note: Analysis done on log-transformed data and the results were back-transformed using anti-logarithms
Test - Group A (Period 1): ESRD subjects (15-mg rivaroxaban administered 2 (±0.5) hours before HD session)
Reference - Group A (Period 2): ESRD subjects (15-mg rivaroxaban administered 3 hours after HD session)
CI= confidence interval, ESRD=end-stage renal disease, HD=hemodialysis

Mean renal clearance (CL_R), clearance by glomerular filtration (CL_{GFR}) and active renal clearance (CL_{ACT}) were approximately 54, 14, and 40 mL/min, respectively, for the normal renal function group. Urinary recovery of rivaroxaban was approximately 39% of the administered dose for the normal renal function group. Due to limited urine collection in ESRD subjects, descriptive statistics were not generated. In the ESRD subjects that were able to produce a limited amount of urine, the amount of rivaroxaban excreted ranged from 0.013% to 3.41% of dose.

PHARMACODYNAMIC RESULTS

Mean absolute PT values in ESRD subjects were higher than the healthy normal subjects. Geometric means for E_{max} and $AUEC_{72}$ values from PT were based on absolute values, change from baseline, and percentage change from baseline. For absolute PT, geometric mean $AUEC_{72}$ was approximately 12% (predialysis) and 8% (postdialysis) higher while geometric mean E_{max} was approximately 16% (predialysis) and 18% (postdialysis) higher for ESRD subjects when compared to the healthy control subjects after receiving a single 15-mg oral dose of rivaroxaban.

Mean percentage change from baseline Factor Xa inhibition exposure for both ESRD groups were higher than the healthy control subjects. Mean percentage change from baseline FXa inhibition values peaked higher in the postdialysis subjects compared to the predialysis subjects; overall, the percentage FXa inhibition time profiles were similar between the 2 groups.

For absolute FXa activity, geometric mean $AUEC_{72}$ decreased by approximately 4% (predialysis) and 14% (postdialysis) while geometric mean E_{max} was higher by approximately 5% (predialysis) and lower by approximately 7% (postdialysis) for ESRD subjects when compared to the healthy control subjects after receiving a single 15-mg oral dose of rivaroxaban.

Mean absolute anti-Factor Xa concentrations peaked higher and faster in the postdialysis subjects compared to the predialysis and healthy control subjects. Overall, exposures were higher in the ESRD groups when compared to the healthy control subjects.

Geometric means for E_{max} and $AUEC_{72}$ values from anti- FXa were based on absolute values. For absolute anti-FXa activity, geometric mean $AUEC_{72}$ was approximately 59% (predialysis) and 61% (postdialysis) higher. Geometric mean E_{max} showed no change for subjects dosed predialysis. However, it was approximately 36% (postdialysis) higher for ESRD subjects when compared to the healthy control subjects after receiving a single 15-mg oral dose of rivaroxaban.

SAFETY RESULTS:

There were no deaths, AEs leading to discontinuation of rivaroxaban, bleeding events or persistent events reported in this study. Adverse events were limited to Group A (clinically stable ESRD subjects). Two of 16 subjects experienced a total of 4 TEAEs; 1 subject had nausea and gingivitis in Period 1 as well as an episode of arteriovenous fistula thrombosis in Period 2. The other subject had nausea only, occurring in Period 1. The investigator considered the event of gingivitis to be moderate in intensity, and all other events were considered to be mild. Both the events of nausea were considered by the investigator to be possibly related to rivaroxaban while the events of gingivitis and arteriovenous fistula thrombosis were considered not related to rivaroxaban. The outcome of all the events was reported as recovered.

One subject, on Study Day 27, had a serious adverse event of arteriovenous fistula thrombosis. The event persisted for approximately 2 hours, was mild in intensity and considered by the investigator to be not related to rivaroxaban. The event had no impact on dosing with rivaroxaban and the outcome of the event was reported as resolved.

For Group A subjects (clinically stable ESRD subjects on hemodialysis), occasional increases or decreases (abnormalities) were observed in the mean values of hematology and/or serum chemistry parameters; none of these changes from the baseline were considered clinically relevant and the changes largely resolved by the end of the study. These abnormalities were considered clinically associated with the documented impairment of renal function in ESRD subjects on chronic hemodialysis.

For Group B subjects (healthy control subjects), the mean changes in the hematology, serum chemistry or coagulation parameters from baseline through various timepoints of assessment were minimal, transient, and not considered clinically relevant.

Overall (for both Group A and Group B subjects) during the study, there were no consistent treatment-related changes observed in the vital sign parameters (ie, systolic and diastolic blood pressure and pulse rate) or ECG measurements.

In order to assess residual renal function in patients from Group A (ESRD subjects on hemodialysis), a 24-hour urine volume on Study Day 1 of Period 1 was calculated and serum creatinine was assessed and CL_{CR} was calculated for subjects who produced ≥50 mL of urine. Of the 8 ESRD subjects (Group A), 5 subjects, were classified as "anuric" with no residual renal function (produced <50 mL of 24-hour urine volume). The remaining 3 ESRD subjects had measured CL_{CR} of 0-, 2-, and 6 mL/min, respectively.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

- Following a single 15-mg oral rivaroxaban dose administered postdialysis in ESRD subjects, rivaroxaban plasma AUC increased by 56% reflecting a 35% decrease in overall clearance due to ESRD.
- Administration of rivaroxaban 2 hours prior to a 4-hour dialysis session resulted in only a 5.5% lowering of plasma AUC and supports dosing of rivaroxaban either prior to or after dialysis.
- Pharmacodynamic changes as assessed by change from baseline in PT, %FXa inhibition, and anti-FXa activity were generally concordant with the observed changes in plasma PK and were higher in ESRD subjects compared to healthy control subjects..
- A single 15-mg dose of rivaroxaban administered in both subjects with ESRD on maintenance hemodialysis and healthy control subjects, was safe and well tolerated with no new safety concerns.

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