SYNOPSIS

Issue Date: 27 June 2012

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

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Protocol No.: RIVAROXACS1001

Title of Study: An Open-Label Study to Estimate the Effect of Multiple-Doses of Erythromycin on the Pharmacokinetics, Pharmacodynamics, and Safety of a Single-Dose of Rivaroxaban in Subjects with Renal Impairment and Normal Renal Function

EudraCT Number: Not applicable

NCT No.: NCT01309438

Clinical Registry No.: CR017968

Coordinating Investigator:

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Study Centers: 4 study sites in USA

Publication (Reference): None

Study Period: First subject in: 17 March 2011 and last subject last visit: 15 March 2012

Phase of Development: 1

Objectives:

The primary objective of this study was to compare the pharmacokinetics (PK) and pharmacodynamics (PD) of JNJ-39039039 (rivaroxaban) (administered as a single 5-mg and 10-mg dose) in subjects with mild or moderate renal impairment receiving multiple doses of erythromycin, to the PK and PD of a single 10-mg dose of rivaroxaban administered alone in subjects with normal renal function.

The secondary objectives were:

- to compare the PK and PD of a single 10-mg dose of rivaroxaban in subjects with normal renal function receiving multiple doses of erythromycin with the PK and PD of a single 10-mg dose of rivaroxaban administered alone in subjects with normal renal function;
- to compare the PK and PD of rivaroxaban (administered as a single 5-mg and 10-mg dose) in subjects with mild or moderate renal impairment receiving multiple doses of erythromycin with the PK and PD of rivaroxaban when administered alone as a single 10-mg dose in subjects with mild or moderate renal impairment, respectively;

- to compare the PK and PD of rivaroxaban when administered alone as a single 10-mg dose in subjects with mild or moderate renal impairment with the PK and PD of rivaroxaban when administered alone as a single 10-mg dose in subjects with normal renal function;
- to assess safety and tolerability.

Methodology:

This was a multicenter, open-label, sequential designed study in healthy subjects with normal renal function, and otherwise healthy subjects with mild or moderate renal impairment. The subjects were assigned to 1 of 3 renal function groups (normal renal function [CL_{CR} >80 mL/min], mild renal impairment [CL_{CR} 50-79 mL/min], or moderate renal impairment [CL_{CR} 30-49 mL/min]) according to their estimated creatinine clearance (CL_{CR}) values, based on Food and Drug Administration (FDA) and Committee for Medicinal Products for Human Use (CHMP) guidelines on PK in subjects with impaired renal function. Group matching was applied to the renal function groups to ensure demographic comparability with respect to gender (approximately the same proportion in each population), mean age (± 10 years), and mean body mass index (BMI ± 20%). Subjects with normal renal function were enrolled after the required numbers of subjects in the mild and moderate renal impairment groups had completed the study. The study consisted of 2 phases: a Screening Phase of approximately 20 days (Day -21 through Day -2) and an open-label treatment phase consisting of either 2 (for normal renal function subjects) or 3 (for subjects with mild or moderate renal impairment) sequential treatment periods. Treatment Period 1 consisted of 4 days, including study drug administration on Day 1 and 48-hour postdose PK and PD blood sample collection ending on Day 3. Treatment Period 2 and Treatment Period 3 consisted of 8 days, including study drug administration from Day 1 to Day 6 and 48-hour postdose PK and PD blood sample collection ending on Day 7. The subjects received rivaroxaban in the morning of Day 1 of Treatment Period 1 and Day 5 of Treatment Period 2 and Treatment Period 3, after at least a 1 hour fast. The subjects received erythromycin 500 mg three times a day (tid) on Days 1 to 6 of Treatment Period 2 and Treatment Period 3.

Number of Subjects (planned and analyzed):

Planned: A total of 24 subjects were planned to be enrolled into 3 renal function groups (normal renal function, mild renal impairment, and moderate renal impairment). Eight subjects were to be enrolled in each group (with at least 3 subjects of each gender per group). Dropouts were to be replaced with subjects (having similar gender, age, and body weight) to ensure that at least 8 subjects completed the study per renal function group.

Analyzed: A total of 29 subjects were enrolled in the study and were included in the safety analyses. A total of 24 subjects completed the study.

Diagnosis and Main Criteria for Inclusion: Men and women between 35 and 75 years of age, inclusive; BMI between 18 and 38 kg/m², inclusive; a body weight of not less than 50 kg and have been characterized as having normal renal function (CL_{CR} >80 mL/min), mild renal impairment (CL_{CR} 50-79 mL/min) or moderate renal impairment (CL_{CR} 30-49 mL/min). Subjects with renal impairment had stable renal disease as determined by the investigator.

Test Product, Dose and Mode of Administration, Batch No.: Rivaroxaban 5-mg (Batch number: 363363, Expiration Date: April 2012) and 10-mg tablet (Batch number: 363364, Expiration Date: April 2012), administered orally.

P-glycoprotein and Moderate Cytochrome P3A4/A5 inhibitor Probe Drug, Dose and Mode of Administration, Batch No.: Erythromycin 500-mg tablet (Batch number: 363963, Expiration Date: July 2013), administered orally.

Treatment regimens:

The following treatment regimens were administered:

- Treatment A: A single 10-mg oral dose of rivaroxaban; in normal renal function, mild renal impairment, and moderate renal impairment groups (Treatment Period 1);
- Treatment B: Erythromycin, 500 mg tid (every 8 hours), administered alone for 4 days, followed by the concomitant administration of erythromycin 500 mg tid, and a single 5 mg dose of rivaroxaban on the fifth day, and a final erythromycin regimen of 500 mg tid continued on Day 6; in the mild and moderate renal impairment groups (Treatment Period 2);
- Treatment C: Erythromycin 500 mg tid, administered alone for 4 days, followed by the concomitant administration of erythromycin 500 mg tid, and a single 10 mg dose of rivaroxaban on the fifth day; and a final erythromycin regimen of 500 mg tid continued on Day 6; in normal renal function (Treatment Period 2) and in the mild and moderate renal impairment groups (Treatment Period 3).

Duration of Treatment: The total study duration for subjects with normal renal function (a 20-day Screening period, one 4-day treatment period, one 8-day treatment period, and one ≤14-day washout period) was approximately 45 days. The total study duration for subjects with impaired renal function (a 20-day Screening period, one 4-day treatment period, two 8-day treatment periods, and two ≤14-day washout periods) was approximately 66 days.

Criteria for Evaluation:

Pharmacokinetics:

During each treatment period, serial blood samples were collected from each subject from 0 to 48 hours after each administration of rivaroxaban for the measurement of rivaroxaban plasma concentrations. The following noncompartmental PK parameters were estimated for each treatment by subject group: C_{max}, t_{max}, AUC_{last}, AUC_{0-48h}, AUC_{∞}, $\%AUC_{\infty,ex}$, $t_{1/2}$, λ_z, CL/F, Vd_z. Additionally, f_u (unbound fraction of rivaroxaban) was measured using a predose sample obtained during Treatment Period 1. Samples were analyzed using a validated, specific, and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

During Treatment Period 2 and Treatment Period 3, trough samples for the measurement of erythromycin plasma concentrations (C_{Trough}) were collected prior to the morning dose administration of erythromycin on Days 2 through 6, with a final sample collected on the morning of Day 7. Trough values from Days 2 through 5 were used for the assessment of steady-state concentrations.

Urine samples were obtained at predetermined intervals up to 48 hours after dosing. The following urinary PK parameters were determined: Ae_{urine}, Ae,%dose, Ae_{t1-t2}, CL_R, CL_{CR} (Cockcroft-Gault estimate from mean serum creatinine), eGFR (Modification of Diet in Renal Disease [MDRD] estimate from mean serum creatinine), CL_{GFR}, CL_{act}, CL_{act}/CL_R, and $CL_{act}/CL/F$.

Pharmacodynamics:

During each treatment period, serial Factor Xa (FXa) activity, Prothrombin time (PT), activated partial thromboplastin time (aPTT), and HepTest® (Heparin in Plasma and Whole Blood) measurements were obtained from each subject prior to and for 48 hours following the administration of rivaroxaban. The following key PD parameters (using the percentage change from baseline) for each of the PD markers were calculated using noncompartmental method by treatment period for each subject group: AUC_{0-48} and E_{max}. Baseline values were defined as the predose (-1 hour) PD sample collection per treatment period.

Pharmacokinetics/Pharmacodynamics:

The relationship between each PD marker (FXa activity, PT, aPTT, and HepTest®) and corresponding rivaroxaban concentrations was characterized.

Pharmacogenomics:

A pharmacogenomic blood sample (10 mL) was collected from the subjects who consented to participate in the optional pharmacogenomic component of the study.

Safety:

Safety and tolerability were evaluated throughout the study via assessment of adverse events (AEs), clinical laboratory tests, 12-lead electrocardiograms (ECGs), vital signs, and physical examinations.

Statistical Methods:

Sample size: Based on study results from the pooled Phase 1 analysis and the results of a previous study in renally impaired subjects, the intersubject coefficients of variation (CV) for PK parameters (AUCs and C_{max}) are estimated to be less than 35%, and the intersubject CVfor PD parameters (AUC_{0-48} and E_{max} for PT) are estimated to be less than 45% for rivaroxaban in subjects with moderate renal impairment and in subjects with normal renal function. Using an estimated intersubject CV of 35% for PK parameters and 45% for PD parameters for rivaroxaban in each renal function group, a sample size of 8 subjects who completed the study in each renal impairment group and 8 completed subjects with normal renal function was considered sufficient for the point estimates of the ratio of mean PK (dose-normalized) and PD parameters of the renally impaired groups versus the normal renal function group subjects to fall within 73.5% to 136.1% and 67.3% to 148.6%, respectively, of its true values with 90% confidence in the following treatment comparisons:

- Treatment B in each renally impaired group versus Treatment A in normal renal function group;
- Treatment C in each renally impaired group versus Treatment A in normal renal function group;
- Treatment A in each renally impaired group versus Treatment A in normal renal function group.

Based on the previous study results from the clarithromycin Drug-Drug Interaction study, the intrasubject CV for the PK parameters (AUCs and C_{max}) was estimated to be less than 15% and the intrasubject CV for the PD parameters (AUC_{0-48} and E_{max} for PT) was estimated to be less than 12% for rivaroxaban in subjects with normal renal function. The same intrasubject CV was assumed for the PK and PD parameters for each renal impairment group. Using an estimated intrasubject CV of 15% for the PK parameters and 12% for the PD parameters for rivaroxaban, a sample size of 8 subjects who completed the study in each renal function group was considered sufficient for the point estimates of the ratio of mean PK and PD parameters to fall within 86.8% to 115.3%, and 89.3% to 112.0%, respectively, of its true values with 90% confidence for the following comparisons:

- Subjects with normal renal function: Treatment C versus Treatment A;
- Subjects with mild renal impairment: Treatment B versus Treatment A;
- Subjects with mild renal impairment: Treatment C versus Treatment A;
- Subjects with moderate renal impairment: Treatment B versus Treatment A;
- Subjects with moderate renal impairment: Treatment C versus Treatment A.

Pharmacokinetics: Based on the rivaroxaban plasma concentration and urine data, the following statistics were calculated for each of the sampling points, by treatment and for the different renal function groups separately: arithmetic mean, standard deviation (SD) and CV, geometric mean, minimum, median,

maximum value and the number of measurements. Individual, composite, and mean concentrations versus time profiles were plotted by treatment and study population using both linear and semi-logarithmic scale. The primary parameters of interest for the statistical analysis were the log-transformed AUCs (AUC_{∞}, AUC_{last}) and C_{max}. Only the data from subjects who completed the study were included in the statistical analysis. If 1 of the PK parameters of interest was not estimable for a given subject in 1 or more periods, the subject's data were not to be included in the statistical analysis of that particular PK parameter. For each log-transformed dose-normalized PK parameter, a mixed effects model was used to estimate the least squares means and intrasubject or intersubject variance; the model included treatment, renal function group and the interaction between treatment and renal function group as fixed effects and subject as a random effect. Using the estimated least squares (LS) means and intrasubject/intersubject variance, the point estimate and 90% confidence intervals (CI) for the difference in means on a log-scale were 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 to reference condition. Comparisons of interest were:

Primary:

- Subjects with mild renal impairment Treatment B versus subjects with normal renal function Treatment A;
- Subjects with mild renal impairment Treatment C versus subjects with normal renal function Treatment A;
- Subjects with moderate renal impairment Treatment B versus subjects with normal renal function Treatment A;
- Subjects with moderate renal impairment Treatment C versus subjects with normal renal function Treatment A.

Secondary:

- Subjects with normal renal function: Treatment C versus Treatment A;
- Subjects with mild renal impairment: Treatment B versus Treatment A and Treatment C versus Treatment A;
- Subjects with moderate renal impairment: Treatment B versus Treatment A and Treatment C versus. Treatment A;
- Subjects with mild renal impairment Treatment A versus subjects with normal renal function Treatment A;
- Subjects with moderate renal impairment Treatment A versus subjects with normal renal function Treatment A.

Attainment of steady-state for erythromycin concentrations was assessed through visual inspection of the concentration-time plots.

Pharmacodynamics: In each study population, descriptive statistics, including arithmetic mean, SD, CV, median, minimum, and maximum were calculated by treatment and study population at each sampling time. Change from baseline in PD measurements was summarized by arithmetic mean, SD, CV, median, minimum, and maximum at each postdose timepoint. The drug effect was characterized by change from baseline values. Individual and mean FXa activity, PT, aPTT, and HepTest® versus time profiles were plotted by treatment and study population for both the actual PD values and the change from baseline for each PD marker. Additional graphical exploration of derived PD parameters as a function of CL_{CR} was performed to compare the PD across the treatment and renal function groups.

The primary parameters of interest for the statistical analysis were the log-transformed estimated $AUC_{0\text{-}48h}$ and E_{max} values. Only the data from subjects who completed the study were included in the

statistical analysis. If 1 of the PD parameters of interest was not estimable for a given subject in 1 or more periods, the subject's data will not be 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 LS means and intrasubject/intersubject variance; the model included treatment, renal function group and the interaction between treatment and renal function group as fixed effects and subject as a random effect. Using the estimated LS means and intra/intersubject variance, the point estimate and 90% CIs for the difference in means on a log scale were constructed. The limits of the CIs were retransformed using antilogarithms to obtain 90% CIs for the ratios of the mean AUC_{0-48h} and E_{max} of the test to reference condition. Comparisons of interest were identical to the same made above in pharmacokinetics.

Pharmacokinetics/Pharmacodynamics: The relationship between each PD marker (FXa activity, PT, aPTT, and HepTest®) and corresponding rivaroxaban concentrations were characterized by using appropriate PK/PD plots. Additional exploratory PK/PD analyses could have been conducted, if deemed appropriate.

Safety: All subjects who received at least 1 dose of the study drug 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 [PT and 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 29 subjects enrolled in the study. Twenty-four subjects completed the study. Of the 5 subjects who were discontinued from the study, 2 (6.9%) were discontinued due to AEs and 2 (6.9%) were discontinued due to other reasons (1 subject discontinued due to a protocol deviation related to erythromycin dosing and 1 subject discontinued due to a positive drug test), all 4 of these subjects were from the mild renal impairment group. One subject (3.4%) from the moderate renal impairment group was discontinued due to withdrawal of consent. There were more women (n=21, 72%) than men (n=8, 28%) and the majority of the subjects were White (23 subjects [79%]) with a mean (SD) age of 62.5 (8.41) years, body weight of 78.87 (16.024) kg, and BMI of 29.07 (4.743) kg/m^2.

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

Pharmacokinetics

In general, compared to subjects with normal renal function, those subjects with mild or moderate renal impairment had higher maximum rivaroxaban plasma concentrations (C_{max}) and higher overall systemic exposures (AUC) when receiving a single 10-mg dose of rivaroxaban. These PK parameters were further increased with the addition of steady-state erythromycin. Specifically, for subjects with moderate renal impairment, the administration of rivaroxaban 10 mg with steady-state erythromycin produced C_{max} and AUC values that were approximately double those values observed in subjects with normal renal function receiving rivaroxaban 10 mg alone. Subjects with mild renal impairment showed a similar trend, however absolute changes in these parameters were slightly less. When administering a 5-mg dose of rivaroxaban with steady-state erythromycin in subjects with either mild or moderate renal impairment, C_{max} and AUC values were very similar to those values observed in subjects with normal renal function receiving rivaroxaban 10 mg alone.

Median t_{max} values were achieved approximately 1 hour earlier in subjects with mild or moderate renal impairment, while their mean $t_{1/2}$ was slightly prolonged by approximately 2 to 3 hours (however these value remained in the typical range for $t_{1/2}$ previously observed).

Consistent with the changes observed with C_{max} and AUC in each renal function group receiving rivaroxaban 10 mg alone, both total apparent clearance (CL/F) and renal clearance (CL_R) decreased with decreasing renal function. While CL/F values were further decreased with the coadministration of steady-state erythromycin, a consistent trend was not observed for the CL_R values. Following the administration of rivaroxaban 10 mg alone, the total amount of drug secreted in the urine (Ae) decreased with decreasing renal function. This trend was also observed with the addition of steady-state erythromycin however with ultimately a higher total amount of unchanged drug recovered in the urine. In addition, the total amount of drug secreted by active renal clearance (CL_{act}) did not appear to change with the addition of erythromycin.

Statistical Analysis of Pharmacokinetic Parameters

For the comparison of the key rivaroxaban PK parameters (AUC_∞, AUC_{last}, and C_{max}) among all 3 treatments, the results from the analysis of variance (ANOVA) and 90% CI for the ratio of PK parameters are presented in the tables below.

Geometric Mean Treatment Ratios (%) and Associated 90% Confidence Intervals- Primary comparisons PK Parameters

(Study RIVAROXACS1001: PK Statistical Analysis Set)

PK	Inter-Subject	N	N	-- Renal Impairment/Function Group and Treatment -		-- Geometric Means --		Ratio	Lower Limit 90%	Upper Limit 90%
Parameter	CV (%)	(Test)	(Ref)	Test	Reference	Test	Reference	(%)	CI (%)	CI (%)
AUC ∞	27	8	8	Mild - Treatment C	Normal - Treatment A	3078.7	1745.5	176.4	136.59	227.77
AUC_{last}	27	8	8	Mild - Treatment C	Normal - Treatment A	2956.7	1708.2	173.1	134.38	222.97
C_{max}	29	8	8	Mild - Treatment C	Normal - Treatment A	277.2	178.17	155.6	118.03	205.07
AUC_∞	27	7	8	Moderate - Treatment C	Normal - Treatment A	3475.5	1745.5	199.1	152.81	259.44
AUC_{last}	27	8	8	Moderate - Treatment C	Normal - Treatment A	3529.1	1708.2	206.6	160.39	266.13
C_{max}	29	8	8	Moderate - Treatment C	Normal - Treatment A	292.42	178.17	164.1	124.51	216.33
AUC_∞	27	8	8	Mild - Treatment B	Normal - Treatment A	3696.4	1745.5	211.8	163.99	273.47
AUC_{last}	27	8	8	Mild - Treatment B	Normal - Treatment A	3526.1	1708.2	206.4	160.25	265.91
C_{max}	29	8	8	Mild - Treatment B	Normal - Treatment A	337.44	178.17	189.4	143.69	249.64
AUC_∞	27	7	8	Moderate - Treatment B	Normal - Treatment A	3648.9	1745.5	209.1	160.44	272.39
AUC_{last}	27	8	8	Moderate - Treatment B	Normal - Treatment A	3723.9	1708.2	218	169.24	280.82
C_{max}	29	8	8	Moderate - Treatment B	Normal - Treatment A	325.94	178.17	182.9	138.79	241.13

Note: Analysis done on log-transformed data and the results were back-transformed using anti-logarithm.
All the PK parameters for rivaroxaban were dose-normalized to 10 mg.
Reference - Treatment A: Rivaroxaban 10mg
Test - Treatment C: Rivaroxaban 10mg + Erythromycin 500mg
Test - Treatment B: Rivaroxaban 5mg + Erythromycin 500mg
(For Treatment B - All the PK parameters for rivaroxaban were dose-normalized to 10 mg)

Primary Objective

Mild Renal Impairment Subjects (Mild-Treatments B and C) versus Normal Renal Function Subjects (Normal-Treatment A)

Compared to subjects with normal renal function receiving rivaroxaban 10 mg alone (Treatment A), subjects with mild renal impairment receiving rivaroxaban 10 mg with steady-state erythromycin (Treatment C) had increases in AUC_∞, AUC_{last}, and C_{max} by approximately 76%, 73%, and 56%, respectively. Similar, although slightly higher increases in the dose-normalized PK parameters were observed with the administration of rivaroxaban 5 mg with steady-state erythromycin (Treatment B)

(ANOVA performed on dose-normalized [to 10 mg] data), in which increases of approximately 112%; 106%, and 89% were observed for AUC_{∞}, AUC_{last}, and C_{max}, respectively.

Moderate Renal Impairment Subjects (Moderate- Treatments B and C) versus Normal Renal Function Subjects (Normal-Treatment A)

Compared to subjects with normal renal function receiving rivaroxaban 10 mg alone (Treatment A), subjects with moderate renal impairment receiving rivaroxaban 10 mg with steady-state erythromycin (Treatment C) had increases in AUC_{∞}, AUC_{last}, and C_{max} by approximately 99%, 107%, and 64%, respectively. Similarly although slightly higher increases in the dose-normalized PK parameters were observed with the administration of rivaroxaban 5 mg with steady-state erythromycin (Treatment B) (ANOVA performed on dose-normalized [to 10 mg] data), in which increases of approximately 109%; 118%, and 83% were observed for AUC_{∞}, AUC_{last}, and C_{max}, respectively.

Geometric Mean Treatment Ratios (%) and Associated 90% Confidence Intervals- Secondary comparisons PK Parameters

(Study RIVAROXACS1001: PK Satistical Analysis Set)

PK	Intra-Subject	N	N	-- Renal Impairment/Function Group and Treatment -		-- Geometric Means --		Ratio	Lower Limit 90%	Upper Limit 90%
Parameter	CV (%)	(Test)	(Ref)	Test	Reference	Test	Reference	(%)	CI (%)	CI (%)
AUC_{∞}	14	8	8	Normal - Treatment C	Normal - Treatment A	2433.5	1745.5	139.4	124.39	156.26
AUC_{last}	14	8	8	Normal - Treatment C	Normal - Treatment A	2397.3	1708.16	140.3	125.28	157.21
C_{max}	16	8	8	Normal - Treatment C	Normal - Treatment A	249.68	178.17	140.1	122.59	160.19
AUC_{∞}	14	8	8	Mild - Treatment C	Mild - Treatment A	3078.7	2001.11	153.9	137.27	172.43
AUC_{last}	14	8	8	Mild - Treatment C	Mild - Treatment A	2956.7	1929.49	153.2	136.79	171.66
C_{max}	16	8	8	Mild - Treatment C	Mild - Treatment A	277.2	219.27	126.4	110.59	144.51
AUC_{∞}	14	7	7	Moderate - Treatment C	Moderate - Treatment A	3475.5	2035.57	170.7	151.14	192.88
AUC_{last}	14	8	8	Moderate - Treatment C	Moderate - Treatment A	3529.1	2150.9	164.1	146.47	183.8
C_{max}	16	8	8	Moderate - Treatment C	Moderate - Treatment A	292.42	242.26	120.7	105.59	137.98
AUC_{∞}	14	8	8	Mild - Treatment B	Mild - Treatment A	3696.4	2001.11	184.7	164.81	207.03
AUC_{last}	14	8	8	Mild - Treatment B	Mild - Treatment A	3526.1	1929.49	182.8	163.14	204.72
C_{max}	16	8	8	Mild - Treatment B	Mild - Treatment A	337.44	219.27	153.9	134.62	175.92
AUC_{∞}	14	7	7	Moderate - Treatment B	Moderate - Treatment A	3648.9	2035.57	179.3	158.69	202.5
AUC_{last}	14	8	8	Moderate - Treatment B	Moderate - Treatment A	3723.9	2150.9	173.1	154.55	193.95
C_{max}	16	8	8	Moderate - Treatment B	Moderate - Treatment A	325.94	242.26	134.5	117.7	153.8
AUC_{∞}	27*	8	8	Mild - Treatment A	Normal - Treatment A	2001.1	1745.5	114.6	88.78	148.05
AUC_{last}	27*	8	8	Mild - Treatment A	Normal - Treatment A	1929.5	1708.16	113	87.69	145.5
C_{max}	29*	8	8	Mild - Treatment A	Normal - Treatment A	219.27	178.17	123.1	93.37	162.22
AUCinf	27*	7	8	Moderate - Treatment A	Normal - Treatment A	2035.6	1745.5	116.6	89.5	151.95
AUClast	27*	8	8	Moderate - Treatment A	Normal - Treatment A	2150.9	1708.16	125.9	97.75	162.2
Cmax	29*	8	8	Moderate - Treatment A	Normal - Treatment A	242.26	178.17	136	103.15	179.22

Note: Analysis done on log-transformed data and the results were back-transformed using anti-logarithm.
* - Inter-Subject CV
Reference – Treatment A: Rivaroxaban 10mg
Test - Treatment B: Rivaroxaban 5mg + Erythromycin 500mg
Test - Treatment C: Rivaroxaban 10mg + Erythromycin 500mg
(For Treatment B - All the PK parameters for rivaroxaban were dose-normalized to 10 mg)

Secondary Objectives

Mild Renal Impairment Subjects (Mild - Treatments B and C) versus Mild Renal Impairment Subjects (Mild - Treatment A)

Compared to subjects with mild renal impairment receiving rivaroxaban 10 mg alone (Treatment A), subjects with mild renal impairment receiving rivaroxaban 10 mg with steady-state erythromycin (Treatment C) had increases in AUC_{∞}, AUC_{last}, and C_{max} by approximately 54%, 53%, and 26%, respectively. Similar, although slightly higher increases in the dose-normalized PK parameters were observed with the administration of rivaroxaban 5 mg with steady-state erythromycin (Treatment B) (ANOVA performed on dose-normalized [to 10 mg] data) in which increases of approximately 85%; 83%, and 54% were observed for AUC_{∞}, AUC_{last}, and C_{max}, respectively.

Moderate Renal Impairment Subjects (Moderate Treatment B and Treatment C) versus Moderate Renal Impairment Subjects (Moderate Treatment A)

Compared to subjects with moderate renal impairment receiving rivaroxaban 10 mg alone (Treatment A), subjects with moderate renal impairment receiving rivaroxaban 10 mg with steady-state erythromycin (Treatment C) had increases in AUC_{∞}, AUC_{last}, and C_{max} by approximately 71%, 64%, and 21%, respectively. Similar, although slightly higher increases in the dose-normalized PK parameters were observed with the administration of rivaroxaban 5 mg with steady-state erythromycin (Treatment B) (ANOVA performed on dose-normalized [to 10 mg] data) in which increases of approximately 79%; 73%, and 34% were observed for AUC_{∞}, AUC_{last}, and C_{max}, respectively.

Subjects with Normal Renal Function - Treatment C versus Treatment A

Compared to subjects with normal renal function receiving rivaroxaban 10 mg alone (Treatment A), subjects with normal renal function receiving rivaroxaban 10 mg with steady-state erythromycin (Treatment C) had increases in AUC_{∞}, AUC_{last}, and C_{max} by approximately 39%, 40%, and 40%, respectively.

Mild and Moderate Renally Impaired Subjects – (Mild/Moderate-Treatment A) versus. Subjects with Normal Renal Function (Normal - Treatment A)

Compared to subjects with normal renal function receiving rivaroxaban 10 mg (Treatment A), subjects with mild renal impairment receiving rivaroxaban 10 mg (Treatment A) had increases in AUC_{∞}, AUC_{last}, and C_{max} by approximately 15%, 13%, and 23%, respectively. Subjects with moderate renal impairment receiving rivaroxaban 10 mg (Treatment A) had increases in AUC_{∞}, AUC_{last}, and C_{max} by approximately 17%, 26%, and 36%, respectively.

Pharmacodynamics

In general for the FXa PD parameter, when compared to subjects with normal renal function, those subjects with mild or moderate renal impairment showed a trend for higher E_{max} and AUC_{0-48} values when receiving a single 10-mg dose of rivaroxaban. These PD parameters were further increased with the addition of steady-state erythromycin. However, these trends were not consistently observed for PT.

Specifically for subjects with moderate renal impairment, the administration of rivaroxaban 10 mg with steady-state erythromycin produced higher FXa E_{max} and AUC_{0-48} values by approximately 36% and 41%, respectively, and higher PT E_{max} and AUC_{0-48} values by approximately 7% and 66%, respectively, than the values observed in subjects with normal renal function receiving rivaroxaban 10 mg alone. Subjects with mild renal impairment showed a similar trend.

When administering a 5-mg dose of rivaroxaban with steady-state erythromycin in subjects with either mild or moderate renal impairment, FXa E_{max}, and AUC_{0-48} values were similar to those values observed in subjects with normal renal function receiving rivaroxaban 10 mg alone. However PT E_{max} and AUC_{0-48} values were generally lower, when the same comparison as above was performed.

Statistical Analysis of Pharmacodynamic Parameters

For the comparison of the key rivaroxaban PD parameters (E_{max} and AUC_{0-48}) among all 3 treatments, the results from the ANOVA and 90% CI for the ratio of PD parameters are presented in the tables below.

Geometric Mean Treatment Ratios (%) and Associated 90% - Confidence Intervals- Primary comparisons PD Parameters

(Study RIVAROXACS1001: PD Stats Analysis Set)

FXa - Summary of the Pairwise Comparison										
PD	Inter-Subject	N	N	-- Renal Impairment/Function Group and Treatment -		-- Geometric Means --		Ratio	Lower Limit 90%	Upper Limit 90%
Parameter	CV (%)	(Test)	(Ref)	Test	Reference	Test	Reference	(%)	CI (%)	CI (%)
AUC_{0-48h}	27	4	8	Mild - Treatment C	Normal - Treatment A	708.5	593.43	119.4	75.39	189.07
E_{max}	15	4	8	Mild - Treatment C	Normal - Treatment A	46.74	39.38	118.7	97.71	144.16
AUC_{0-48h}	27	8	8	Moderate - Treatment C	Normal - Treatment A	842.3	593.43	141.9	97.52	206.59
E_{max}	15	8	8	Moderate - Treatment C	Normal - Treatment A	53.61	39.38	136.1	116.13	159.54
AUC_{0-48h}	27	4	8	Mild - Treatment B	Normal - Treatment A	697.7	593.43	117.6	74.24	186.18
E_{max}	15	4	8	Mild - Treatment B	Normal - Treatment A	40.43	39.38	102.7	84.51	124.68
AUC_{0-48h}	27	8	8	Moderate - Treatment B	Normal - Treatment A	512.3	593.43	86.32	59.31	125.65
E_{max}	15	8	8	Moderate - Treatment B	Normal - Treatment A	38.56	39.38	97.91	83.54	114.76
PT - Summary of the Pairwise Comparison										
PD	Inter-Subject	N	N	-- Renal Impairment/Function Group and Treatment -		-- Geometric Means --		Ratio	Lower Limit 90%	Upper Limit 90%
Parameter	CV (%)	(Test)	(Ref)	Test	Reference	Test	Reference	(%)	CI (%)	CI (%)
AUC_{0-48h}	31	8	8	Mild - Treatment C	Normal - Treatment A	118.7	67.82	175	115.32	265.42
E_{max}	41	8	8	Mild - Treatment C	Normal - Treatment A	9.85	8.24	119.5	79.73	179.18
AUC_{0-48h}	31	8	8	Moderate - Treatment C	Normal - Treatment A	115.1	67.82	169.8	111.9	257.55
E_{max}	41	8	8	Moderate - Treatment C	Normal - Treatment A	10.02	8.24	121.6	81.11	182.28
AUC_{0-48h}	31	7	8	Mild - Treatment B	Normal - Treatment A	62.05	67.82	91.49	59.62	140.38
E_{max}	41	7	8	Mild - Treatment B	Normal - Treatment A	7	8.24	84.89	56.3	128.01
AUC_{0-48h}	31	8	8	Moderate - Treatment B	Normal - Treatment A	60.69	67.82	89.49	58.99	135.77
E_{max}	41	8	8	Moderate - Treatment B	Normal - Treatment A	5.25	8.24	63.67	42.47	95.46

Note: Analysis done on log-transformed data and the results were back-transformed using anti-logarithm.
Reference - Treatment A: Rivaroxaban 10mg
Test - Treatment C: Rivaroxaban 10mg + Erythromycin 500mg
Test - Treatment B: Rivaroxaban 5mg + Erythromycin 500mg
(For Treatment B - All the PD parameters for rivaroxaban were non-dose-normalized)

Primary Objective:

Mild Renal Impairment Subjects (Mild-Treatments B and C) versus Normal Renal Function Subjects (Normal-Treatment A)

Compared to subjects with normal renal function receiving rivaroxaban 10 mg alone (Treatment A), subjects with mild renal impairment receiving rivaroxaban 10 mg with steady-state erythromycin (Treatment C) had increases in FXa AUC_{0-48h} and E_{max} values by approximately 19% and increases in PT AUC_{0-48h} and E_{max} values by approximately 75% and 20%, respectively. Additionally, the same comparison was made with a 5-mg dose of rivaroxaban with steady-state erythromycin (Treatment B), in which increases of approximately 17% and 3% were observed for non-dose-normalized FXa AUC_{0-48h}

and E_{max} values and decreases of approximately 9%, and 15% for non-dose-normalized PT AUC_{0-48h} and E_{max} values, respectively, were observed as shown in table above. Similar trends were also observed for aPTT and HepTest®.

Moderate Renal Impairment Subjects (Moderate- Treatments B and C) versus Normal Renal Function Subjects (Normal-Treatment A)

Compared to subjects with normal renal function receiving rivaroxaban 10 mg alone (Treatment A), subjects with moderate renal impairment receiving rivaroxaban 10 mg with steady-state erythromycin (Treatment C) had increases in FXa AUC_{0-48h} and E_{max} values by approximately 42% and 36%, respectively, and increases in PT AUC_{0-48h} and E_{max} values by approximately 70% and 22%, respectively. Additionally, the same comparison was made with a 5-mg dose of rivaroxaban with steady-state erythromycin (Treatment B), in which decreases of approximately 14% and 2% were observed for non-dose-normalized FXa AUC_{0-48h} and E_{max} values and decreases of approximately 11% and 36% for non-dose-normalized PT AUC_{0-48h}, and E_{max} values, respectively, were observed as shown in table above. Similar trends were also observed for aPTT and HepTest®.

Geometric Mean Treatment Ratios (%) and Associated 90% Confidence Intervals- Secondary comparisons PD Parameters

(Study RIVAROXACS1001: PD Stats Analysis Set)

FXa - Summary of the Pairwise Comparison										
PD	Intra-Subject	N	N	-- Renal Impairment/Function Group and Treatment -		-- Geometric Means --		Ratio	Lower Limit 90%	Upper Limit 90%
Parameter	CV (%)	(Test)	(Ref)	Test	Reference	Test	Reference	(%)	CI (%)	CI (%)
AUC_{0-48h}	37	8	8	Normal - Treatment C	Normal - Treatment A	547.6	593.43	92.28	67.95	125.32
E_{max}	12	8	8	Normal - Treatment C	Normal - Treatment A	46.4	39.38	117.8	106.53	130.27
AUC_{0-48h}	37	4	4	Mild - Treatment C	Mild - Treatment A	708.5	690.5	102.6	66.56	158.18
E_{max}	12	4	4	Mild - Treatment C	Mild - Treatment A	46.74	46.17	101.3	87.82	116.72
AUC_{0-48h}	37	8	8	Moderate - Treatment C	Moderate - Treatment A	842.3	611.09	137.8	101.49	187.18
E_{max}	12	8	8	Moderate - Treatment C	Moderate - Treatment A	53.61	45.94	116.7	105.52	129.04
AUC_{0-48h}	27*	4	8	Mild - Treatment A	Normal - Treatment A	690.5	593.43	116.4	73.48	184.27
E_{max}	15*	4	8	Mild - Treatment A	Normal - Treatment A	46.17	39.38	117.2	96.51	142.38
AUC_{0-48h}	27*	8	8	Moderate - Treatment A	Normal - Treatment A	611.1	593.43	103	70.75	149.88
E_{max}	15*	8	8	Moderate - Treatment A	Normal - Treatment A	45.94	39.38	116.7	99.52	136.72
AUC_{0-48h}	37	4	4	Mild - Treatment B	Mild - Treatment A	697.7	690.5	101	65.54	155.76
E_{max}	12	4	4	Mild - Treatment B	Mild - Treatment A	40.43	46.17	87.57	75.96	100.95
AUC_{0-48h}	37	8	8	Moderate - Treatment B	Moderate - Treatment A	512.3	611.09	83.83	61.73	113.84
E_{max}	12	8	8	Moderate - Treatment B	Moderate - Treatment A	38.56	45.94	83.94	75.9	92.82
PT - Summary of the Pairwise Comparison										
PD	Intra-Subject	N	N	-- Renal Impairment/Function Group and Treatment -		-- Geometric Means --		Ratio	Lower Limit 90%	Upper Limit 90%
Parameter	CV (%)	(Test)	(Ref)	Test	Reference	Test	Reference	(%)	CI (%)	CI (%)
AUC_{0-48h}	41	8	8	Normal - Treatment C	Normal - Treatment A	82.75	67.82	122	87.61	169.96
E_{max}	27	8	8	Normal - Treatment C	Normal - Treatment A	9.1	8.24	110.3	87.82	138.65
AUC_{0-48h}	41	8	8	Mild - Treatment C	Mild - Treatment A	118.7	99.46	119.3	85.64	166.16
E_{max}	27	8	8	Mild - Treatment C	Mild - Treatment A	9.85	8.63	114.1	90.84	143.42
AUC_{0-48h}	41	8	8	Moderate - Treatment C	Moderate - Treatment A	115.1	64.23	179.3	128.69	249.67
E_{max}	27	8	8	Moderate - Treatment C	Moderate - Treatment A	10.02	8.34	120.2	95.67	151.04
AUC_{0-48h}	31*	8	8	Mild - Treatment A	Normal - Treatment A	99.46	67.82	146.7	96.67	222.5
E_{max}	41*	8	8	Mild - Treatment A	Normal - Treatment A	8.63	8.24	104.7	69.85	156.98
AUC_{0-48h}	31*	8	8	Moderate - Treatment A	Normal - Treatment A	64.23	67.82	94.71	62.43	143.68
E_{max}	41*	8	8	Moderate - Treatment A	Normal - Treatment A	8.34	8.24	101.2	67.48	151.64
AUC_{0-48h}	41	7	8	Mild - Treatment B	Mild - Treatment A	62.05	99.46	62.38	44.14	88.16
E_{max}	27	7	8	Mild - Treatment B	Mild - Treatment A	7	8.63	81.07	63.81	103
AUC_{0-48h}	41	8	8	Moderate - Treatment B	Moderate - Treatment A	60.69	64.23	94.5	67.84	131.62
E_{max}	27	8	8	Moderate - Treatment B	Moderate - Treatment A	5.25	8.34	62.95	50.1	79.09

Note: Analysis done on log-transformed data and the results were back-transformed using anti-logarithm.
* - Inter-Subject CV
Reference - Treatment A: Rivaroxaban 10mg
Test - Treatment C: Rivaroxaban 10mg + Erythromycin 500mg
Test - Treatment B: Rivaroxaban 5mg + Erythromycin 500mg
(For Treatment B - All the PD parameters for rivaroxaban were non-dose-normalized)

Secondary Objectives:

Mild Renal Impairment Subjects (Mild Treatments B and C) versus Mild Renal Impairment Subjects (Mild - Treatment A)

Compared to subjects with mild renal impairment receiving rivaroxaban 10 mg alone (Treatment A), subjects with mild renal impairment receiving rivaroxaban 10 mg with steady-state erythromycin (Treatment C) had very slight increases in FXa $AUC_{0\text{-}48h}$ and E_{max} values by approximately 3% and 1%, respectively, and increases in PT $AUC_{0\text{-}48h}$ and E_{max} values by approximately 19% and 14%, respectively. Additionally, the same comparison was made with a 5-mg dose of rivaroxaban with steady-state erythromycin (Treatment B), in which an increase of approximately 1% and a decrease of approximately 12% was observed for non-dose-normalized FXa $AUC_{0\text{-}48h}$ and E_{max} values and decreases of approximately 38% and 19% were observed for non-dose-normalized PT $AUC_{0\text{-}48h}$ and $E_{max,}$ values, respectively. Similar trends were also observed for aPTT and HepTest®.

Moderate Renal Impairment Subjects (Moderate Treatments B and C) versus Moderate Renal Impairment Subjects (Moderate Treatment A)

Compared to subjects with moderate renal impairment receiving rivaroxaban 10 mg alone (Treatment A), subjects with moderate renal impairment receiving rivaroxaban 10 mg with steady-state erythromycin (Treatment C) had increases in FXa $AUC_{0\text{-}48h}$ and E_{max} values by approximately 38% and 17%, respectively, and increases in PT $AUC_{0\text{-}48h}$ and E_{max} values by approximately 79% and 20%, respectively. Additionally, the same comparison was made with a 5-mg dose of rivaroxaban with steady-state erythromycin (Treatment B), in which decreases of approximately 16% were observed for non-dose-normalized FXa $AUC_{0\text{-}48h}$ and E_{max} values and decreases of approximately 5% and 37% were observed for non-dose-normalized PT $AUC_{0\text{-}48h}$ and $E_{max,}$ values respectively. Similar trends were also observed for aPTT and HepTest®.

Subjects with Normal Renal Function - Treatment C versus Treatment A

Compared to subjects with normal renal function receiving rivaroxaban 10 mg alone (Treatment A), subjects with normal renal function receiving rivaroxaban 10 mg with steady-state erythromycin (Treatment C) displayed a slight reduction in FXa $AUC_{0\text{-}48h}$ (by approximately 8%) while displaying and increase in E_{max} of approximately 18%. PT displayed increases in $AUC_{0\text{-}48h}$ and E_{max} by approximately 22% and 10% respectively. Similar trends were also observed for aPTT and HepTest®.

Mild and Moderate Renally Impaired Subjects –(Mild/Moderate-Treatment A) versus Subjects with Normal Renal Function (Normal - Treatment A)

Compared to subjects with normal renal function receiving rivaroxaban 10 mg (Treatment A), subjects with mild renal impairment receiving rivaroxaban 10 mg (Treatment A), had increases in FXa $AUC_{0\text{-}48h}$ and E_{max} values by approximately 16% and 17%, respectively, and increases in PT $AUC_{0\text{-}48h}$ and E_{max} values by approximately 47% and 5%, respectively. Subjects with moderate renal impairment receiving rivaroxaban 10 mg (Treatment A) had very slight increases in FXa $AUC_{0\text{-}48h}$ and E_{max} values by approximately 3% and 17%, respectively, While PT $AUC_{0\text{-}48h}$ and E_{max} values did not appear to significantly change. Changes in aPTT and Heptest® were inconsistent, and similar trends were not observed.

Pharmacogenomics

No data was analyzed at present. If an analysis of the pharmacogenomic component of the study is performed, results will be reported separately.

SAFETY RESULTS:

A total of 21 (72.41%) of the 29 subjects who received at least 1 dose of study drug, reported 1 or more treatment-emergent AEs (TEAEs). The incidence of TEAEs was 8 (88.9%) in subjects with moderate renal impairment, 10 (83.3%) in subjects with mild renal impairment, and 3 (37.5%) in subjects with normal renal function. The most common TEAEs by system organ class reported in all renal function groups were Gastrointestinal Disorders followed by Nervous System Disorders, and Musculoskeletal and Connective Tissue Disorders. The incidence of TEAEs in each renal function group was higher with the administration of erythromycin 500 mg tid alone, than with the administration of rivaroxaban 10 mg alone. There were no TEAEs reported with the coadministration of erythromycin 500 mg tid + rivaroxaban 10 mg in the normal renal function group and no TEAEs reported with the coadministration of erythromycin 500 mg tid + rivaroxaban 5 mg nor with the coadministration of erythromycin 500 mg tid + rivaroxaban 10 mg, in the mild renal impairment group. In the moderate renal impairment group, TEAEs were reported with all 3 treatment regimens. The most common TEAEs reported across all renal function groups were abdominal pain, diarrhea, and dizziness which were reported mainly with the administration of erythromycin 500 mg tid. Nausea and headache were other TEAEs commonly reported in the mild and moderate renal impairment groups, which again, reported mainly with the administration of erythromycin 500 mg tid. All TEAEs reported in the mild renal impairment group were considered by the investigator as not related to study drug except dizziness and somnolence which were considered as very likely related to the rivaroxaban. All TEAEs reported in the mild renal impairment group were considered by the investigator as not related to study drug, except diarrhea, muscle spasm, myalgia, and headache (1 event each, all possibly related to rivaroxaban), nausea and abdominal pain (1 event each all probably related to rivaroxaban), nausea, abdominal pain, constipation, abdominal distension, and chest discomfort (1 event each, all possibly related to erythromycin), and nausea (3 events), abdominal pain (2 events), vomiting (2 events), diarrhea, constiptation, and dyspepsia (1 event each) (all probably related to erythromycin). All TEAEs reported in the moderate renal impairment group were considered by the investigators as not related or doubtfully related to study drug except diarrhea (3 events), abdominal pain (2 events), and headache (3 events), all possibly related to rivaroxaban; 1 event of gingival bleeding which was probably related to rivaroxaban; 1 event of nausea which was possibly to erythromycin; and 1 event each of dysgeusia and vulvovaginal mycotic infection which were probably to erythromycin.

No deaths or treatment-emergent serious AEs (SAEs) occurred during this study. One subject in the moderate renal impairment group had an SAE of congestive cardiac failure during the Screening Period. The subject was excluded from enrollment in the study, and never received the study drug. Two subjects (6.9%) in the mild renal impairment group were discontinued from the study due to AEs of nausea and vomiting.

The following AEs of clinical interest were observed: One subject in the normal renal function group, who was enrolled in the study and developed an AE of hematoma 4 days after receiving rivaroxaban 10 mg alone in Treatment Period 1 (bleeding event). Three subjects in the moderate renal impairment group reported bleeding events: One subject, who was enrolled in the study and experienced an AE of hemoptysis, one day after receiving rivaroxaban 10 mg on Day 1 of Treatment Period 1. Another subject, who was enrolled in the study and developed an AE of skin lesion on her right ear lobe 18 days after receiving the last dose of erythromycin on Day 6 of Treatment Period 2. The third subject, who was enrolled in the study and experienced AEs of vessel puncture site hemorrhage (2 episodes), injection site hemorrhage, gingival bleeding, and infusion site extravasation. The investigator considered all these events as mild in intensity and not related to rivaroxaban and erythromycin, except the event of skin lesion which was considered as doubtfully related to rivaroxaban and erythromycin and the event of gingival bleeding, which was considered as probably related to rivaroxaban. No action was taken with regard to study drug due to these AEs. All AEs were reported as resolved during the study. No bleeding events were observed in the mild renal impairment group. No liver-related AEs were reported during the study in any treatment group.

A small decrease in mean hemoglobin (Hb) concentration from baseline was noted in the normal renal function group on Treatment Period 2, Day -1 and on all treatment periods in the mild renal impairment group. No notable changes were observed in the moderate renal impairment group. A small increase from baseline mean platelet count was noted in the mild and moderate renal impairment groups on Day -1 of Treatment Period 3. No notable changes were observed in the normal renal function group.

A slight increase from baseline was observed in mean values for all liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin) and at the end-of-study (EOS) visit in all renal function groups except AST in the mild impairment group and bilirubin in normal renal function group.

While serial PT and aPTT samples were collected throughout the study as a PD marker, spot checks for real-time safety assessments were also collected with and without the other safety laboratory assessments. At the time these samples were collected, small mean increases from baseline were observed for aPTT across all renal function groups. The same trend was observed for PT in the normal renal function group, while in the mild renal impairment group, a small mean decrease was noted in PT levels from baseline in Treatment Period 1, and a small mean increase was observed from baseline to Treatment Period 2. Finally, a small mean increase in PT level was noted from baseline to EOS visit in the moderate renal impairment group.

Seven subjects in the normal renal function group, 12 subjects in the mild renal impairment group, and 9 subjects in the moderate renal impair group had abnormal laboratory (hematology, chemistry, and coagulation) values noted during the study. However these abnormal laboratory values were not considered to be clinically significant.

No clinically meaningful changes in the mean body weight, BMI, physical examination abnormalities, and vital signs value (pulse rate, blood pressure, and oral temperature) were observed.

STUDY LIMITATIONS: No notable study limitations were identified by the sponsor.

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