

A Cross-Study Analysis Evaluating the Effects of Food on the Pharmacokinetics of Rivaroxaban in Clinical Studies

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Abstract

US prescribing guidelines recommend that 15- and 20-mg doses of rivaroxaban be administered with food for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for reduction in the risk of recurrence of DVT and PE. In addition, the US prescribing guidelines recommend these doses be administered with an evening meal to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). The purpose of this model-based cross-study comparison was to examine the impact of food, with regard to both meal timing and content, on the pharmacokinetics (PK) of rivaroxaban, using data collected during its clinical development. Results of this analysis showed that a PK model built from pooled data in the AF population (for whom rivaroxaban was administered with an evening meal) and in the DVT population (for whom rivaroxaban was administered with a morning meal) can describe both data sets well. Furthermore, the PK model built from data in the AF population alone can adequately predict the PK profile of the DVT population and vice versa. This cross-study analysis also confirmed the findings from previous clinical pharmacology studies, which showed that meal content does not have a clinically relevant impact on the PK of rivaroxaban at 20 mg. Therefore, although the administration of rivaroxaban with food is necessary for maintaining high bioavailability, neither meal timing nor meal content appears to affect the PK of rivaroxaban.

Keywords

rivaroxaban, pharmacokinetics, food effect, bioavailability

Rivaroxaban (JNJ 39039039, BAY 59–7939, Xarelto) is a potent and highly selective oral direct factor Xa inhibitor. Rivaroxaban has been approved for multiple indications worldwide and is approved in the United States for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF), for treating deep vein thrombosis (DVT) and pulmonary embolism (PE), for reducing the risk of recurrence of DVT and PE, and for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.¹ The recommended rivaroxaban dosage for the AF indication is 20 mg once daily (15 mg for patients with creatinine clearance [CrCl] of 15–50 mL/min) with the evening meal. For the treatment of DVT and PE and long-term reduction in the risk of recurrence of DVT and PE, the recommended dose is 15 mg orally twice daily with food for the first 21 days, followed by 20 mg orally once daily with food for the remaining time on treatment.^{1,2} Given the different recommendations regarding food intake across these 2 indications (taking with food versus taking with the evening meal), it is of interest to study the impact of meal timing and meal content on the pharmacokinetics (PK) of rivaroxaban.

Well-controlled clinical pharmacology studies in healthy adult subjects have been conducted to evaluate the impact of food intake on the PK characteristics of rivaroxaban. These studies showed that the oral

bioavailability of rivaroxaban is generally high. For the 10-mg tablet, almost complete oral absorption was observed in both fed and fasting conditions.³ For the 20-mg tablet, the oral bioavailability was shown to be approximately 66% under fasting conditions, whereas under fed conditions, the oral bioavailability of the 20-mg tablet was almost complete (area under the plasma concentration–time curve [AUC] increased by 39%).³ The effect of meal content on rivaroxaban PK was also formally assessed in dedicated clinical pharmacology studies prior to the large, pivotal phase 3 studies. The meal content followed the recommendations outlined by the US Food and Drug Administration (FDA) Guidance for Industry,⁴ in which a high-fat, high-calorie meal was consumed with rivaroxaban after fasting overnight. In addition to these dedicated

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Table 1. Phase 2 and Phase 3 Studies of Rivaroxaban for DVT and AF Included in the Current Analysis

Study	n	Dose ^a	Food Recommendations	Primary Outcome
EINSTEIN-DVT dose-ranging phase 2 study ⁶	543	Rivaroxaban 20, 30, or 40 mg or LMWH/VKA	Take with morning meal (type or amount unspecified)	Composite efficacy outcome ^b : 6.1%, 5.4%, 6.6%, 9.9%, respectively
ROCKET AF phase 3 study ¹¹	14 264	Rivaroxaban 20 mg (15 mg for patients with CrCl 30–49 mL/min) or warfarin	Take with evening meal (type or amount unspecified)	Composite of stroke and systemic embolism: 1.7% vs 2.2%

DVT, deep vein thrombosis; AF, atrial fibrillation; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; CrCl, creatinine clearance; PE, pulmonary embolism.

^aRivaroxaban was administered once daily.

^b3-month incidence of the composite of symptomatic recurrent DVT, symptomatic fatal or nonfatal PE, and asymptomatic deterioration in thrombotic burden.

Table 2. Demographic Characteristics of Patients in the DVT Data Set and AF Data Set^{12,13}

Data Set ^a	DVT Data (n = 124) ^b	AF Data (n = 161) ^c
PK sampling scheme	8 samples collected from each patient 1–6 hours postdose at 2 visits or 3 samples collected from each patient predose and 2–6 hours postdose at 3 visits	5 samples collected from each patient predose and 1–16 hours postdose at 2 visits
Age (years)	59 (31, 83)	65 (51, 81)
Baseline SCr (mg/dL)	0.94 (0.64, 1.28)	1.05 (0.74, 1.65)
Lean body mass (kg)	54.1 (40.1, 72.7)	56.6 (42.5, 73.6)

DVT, deep vein thrombosis; AF, atrial fibrillation; PK, pharmacokinetics; SCr, serum creatinine concentration.

^aValues represent median (5th and 95th percentiles).

^bA total of 124 patients received rivaroxaban 20 mg once daily and had evaluable PK information.

^cA total of 161 patients received rivaroxaban 20 mg once daily (n = 136) or 15 mg once daily (n = 25) and had evaluable PK information.

food-effect studies, other clinical pharmacology studies that specified high-carbohydrate and liquid nutritional supplement meals were conducted, allowing for indirect comparisons of different meal types.⁵

In subsequent global, phase 2 and 3 studies that assessed the use of rivaroxaban in patients with DVT, PE, or AF, the timing and content of the meals with which rivaroxaban was administered varied.^{6–11} Although general guidelines were given regarding when to take the dose with a meal, the nature of these global studies inherently provided differences in meal timing, type, and quantity. Population PK analyses quantifying rivaroxaban exposure in several of these clinical studies were performed^{12,13} and findings from these separate analyses were generally consistent. Considering the diversity in the patient populations in global clinical trials, a cross-study comparison assessing rivaroxaban exposure in later-phase clinical studies would enhance our understanding of the potential impact of meal intake, with regard to the timing and content, in real-world patient care. Hence, the aim of this model-based cross-study comparison was to evaluate the impact of food on the PK of rivaroxaban, using data collected from 2 late-stage clinical studies: a global

phase 2 study for the treatment of acute symptomatic proximal DVT, in which patients were instructed to take rivaroxaban with a morning meal,⁶ and a global phase 3 study for AF, in which rivaroxaban was administered once daily with an evening meal.¹¹

Methods

For all the studies described in this article, written informed consent was obtained from all subjects. These studies were performed according to the principles of the Declaration of Helsinki, as well as good clinical practice guidelines, therapeutic products program regulations, and applicable FDA and investigational new drug regulations.^{6,11} Study protocols were approved by relevant national regulatory authorities and ethics committees and local institutional review boards at participating study centers.^{6,11}

Data

Phase 2 DVT Study. The EINSTEIN-DVT dose-ranging study⁶ (once-daily oral direct factor Xa inhibitor BAY 59–7939 in patients with acute deep-vein thrombosis) was a phase 2 study that evaluated the

dose–effect relationship of rivaroxaban administered once daily to patients diagnosed with acute symptomatic DVT. Patients ($n = 543$) were randomized to receive either a combination of low-molecular-weight heparin with a vitamin K antagonist or rivaroxaban (Table 1). Patients randomized to rivaroxaban received doses of 20, 30, or 40 mg, which were administered once daily with a morning meal for a duration of 12 weeks. Neither the amount nor the type of food that would accompany the rivaroxaban dose was prespecified. Results from the EINSTEIN-DVT study demonstrated the initial efficacy and safety of rivaroxaban for the treatment of acute symptomatic DVT.⁶ In addition, there was no dose–response relationship observed for rivaroxaban with respect to its efficacy.⁶ In this study, PK samples were collected predose and 2 to 6 hours postdose on study day 1, predose on study day 43, and 2 to 6 hours postdose on day 84. Previously, a population PK modeling analysis was performed based on the pooled PK data from 2 phase 2 studies of similar design: the EINSTEIN-DVT dose-ranging study that is described here⁶ and the ODIXa-DVT study (Oral Direct Factor Xa Inhibitor BAY 59–7939 in Patients with acute symptomatic Deep Vein Thrombosis).⁷ The PK model generated from this analysis is referred to as the DVT model from this point forward.¹³

Phase 3 AF Study. The ROCKET AF study (Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) was a prospective, randomized, double-blind, double-dummy, parallel-group, active-controlled, multicenter, event-driven phase 3 study that compared the efficacy and safety of rivaroxaban with warfarin for the prevention of stroke and non-central nervous system (CNS) systemic embolism in patients with nonvalvular AF (Table 1).¹¹ Patients ($n = 14\,264$) were assigned to rivaroxaban 20 mg once daily (15 mg in patients with CrCl of 30–49 mL/min) or to warfarin titrated to a target international normalized ratio of 2.5 (range, 2.0–3.0, inclusive) and were treated for a median follow-up of approximately 700 days and median exposure of approximately 590 days. Patients were instructed to take their dose of rivaroxaban with their evening meal, given the assumption that the evening meal would be the subject’s largest meal of the day, at least in North America, thereby maximizing the desired food effect for the 15- and 20-mg doses. The results of the ROCKET AF study showed that rivaroxaban was noninferior to warfarin for preventing stroke and non-CNS embolism.¹¹ In the ROCKET AF study, PK samples were collected from a subset of patients ($n = 161$) at steady state; 3 samples (predose, 1–3 hours postdose, and 3–16 hours postdose) were collected

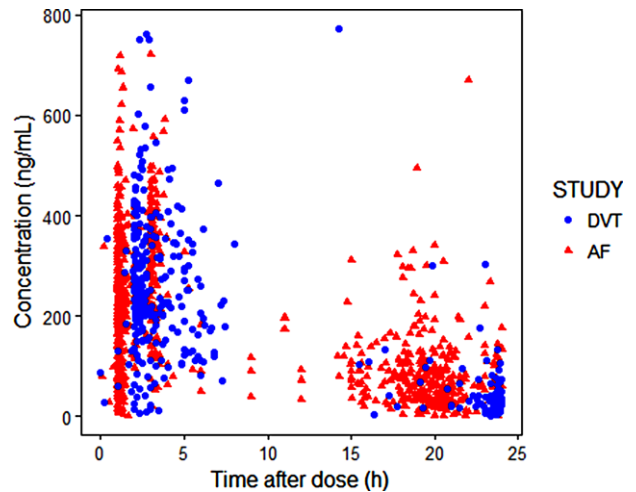


Figure 1. Concentration-versus-time profiles of rivaroxaban at 20 mg once daily. DVT, deep vein thrombosis; AF, atrial fibrillation; CrCl, creatinine clearance; 15 mg for patients with CrCl of 15–49 mL/min in AF data. Blue dots, DVT data; red triangles, AF data.

on a convenient day between week 2 and the end-of-study visit, and 2 samples (predose and 1–3 hours postdose) were collected in a subsequent visit at least 1 month afterward. The population PK model that was developed using this data set is referred to as the AF model from this point forward.¹²

Model-Based Method for Cross-Study PK Comparison

To account for the inherent differences between the 2 studied populations in terms of sampling scheme and patient characteristics, 2 model-based approaches were used for the cross-study comparisons of the rivaroxaban PK characteristics after the administration of a 20-mg once-daily dose within both the phase 2 EINSTEIN-DVT dose-ranging and the phase 3 ROCKET AF studies.^{12,13} The cross-study comparison between rivaroxaban levels in the EINSTEIN-DVT and ROCKET AF data could help to evaluate the impact of meal timing on the PK parameters of rivaroxaban (eg, evening meal versus morning meal). In the ROCKET AF study, patients who received rivaroxaban 15 mg once daily (CrCl, 30–49 mL/min) had similar exposure to those who received rivaroxaban 20 mg once daily (CrCl ≥ 50 mL/min)¹²; thus, patients receiving these 2 doses were taken as 1 group representing the AF patient population for the purposes of the current analysis. The data sets included in this analysis are referred as the DVT data and AF data, respectively, from this point forward. Key features of the 2 data sets are summarized in Table 2. In general, patients included in the AF data were older and had higher serum creatinine levels compared with those included in the DVT data. Figure 1 shows the concentration-versus-time profile of each data set.

Joint PK Model for DVT and AF Studies. Nonlinear mixed-effects population modeling was used to build a joint PK model using both the DVT data and the AF data and to test the potential difference between the 2 populations. Similar to the DVT and AF models,^{12,13} the joint-based model was a 1-compartment model, parameterized in terms of apparent plasma clearance after oral administration (CL/F), apparent volume of distribution after oral administration (V/F), and a first-order absorption rate constant (k_a). Age and serum creatinine concentration were included as covariates on CL/F and, likewise, age and lean body mass on V/F. Interindividual variability (IIV) terms were incorporated in exponential format on CL/F and V/F. A proportional error model was used to describe the random residual error. The significance of study-specific terms on the relative bioavailability (F1) and CL/F were examined using the likelihood ratio test with a critical level of $P < .05$. Model evaluations included graphical inspection of basic goodness-of-fit plots, reduction in objective function values, visual predictive checks, and the precision of parameter estimates. The analyses were performed using NONMEM 7.2 software (ICON Development Solutions, Hanover, Maryland) with the first-order conditional estimation method with interaction. Additional statistics and graphs were generated using R 3.2.2.

Simulation for Cross-Study PK Comparison. A second model-based comparison between the DVT data and AF data was conducted using the AF model with the dosing and demographic information obtained from the DVT data. This comparison led to the simulation of individual rivaroxaban exposures, as measured by the PK parameters AUC over a dosing interval at steady state, maximum plasma concentration (C_{max}) of the drug, CL/F, and V/F, for the patients in the DVT data set. These simulated values can be considered the same as those expected in the DVT population, if there was no difference in the PK characteristics in the AF and DVT populations and if patients took their dose of rivaroxaban with an “evening meal.” The simulated values were then compared with the values estimated from the DVT model. Likewise, the DVT model and the dosing and demographic information obtained from the ROCKET AF data were used to simulate the AUC, C_{max} , CL/F, and V/F parameters for patients in the ROCKET AF data set. These simulated values can be considered the same as those expected in the ROCKET AF population, if there was no difference in the PK characteristics in the AF and DVT populations and if patients took their dose of rivaroxaban with a “morning meal.” The simulated values were then compared with the values estimated from the ROCKET AF model.

Based on the DVT and AF models, rivaroxaban PK parameters and exposure levels in individual patients, including the parameters CL/F, V/F, AUC, and C_{max} , were estimated for each population and subsequently compared with the simulated data, as described above.

Results

Joint PK Model for DVT and AF Studies

A joint PK model was built using the DVT and AF data sets. Using a base model similar to the DVT and AF models, the model reestimated all PK parameters and tested the statistical significance of relative bioavailability between the 2 input data sets. Table 3 lists the estimated parameter values from the joint model, which were compared with those from the DVT and AF models. All parameters were estimated with good precision; the IIV of CL/F and V/F was moderate (coefficients of variation, 34.6% and 15.5%, respectively). The residual variability of the model was 47.5%. Goodness of fit of the PK model was evaluated using a graphic approach (Figure 2), which confirmed the validity of the joint model and showed that the joint model could adequately describe the DVT and AF data.

In general, the parameter estimates from the joint model were similar to those reported for the DVT and AF models (Table 3).^{12,13} To evaluate the potential impact of different instructions concerning dose administration with food on the degree of absorption for the 2 indications, the joint model estimated the bioavailability of the DVT data (in which rivaroxaban was administered with a morning meal) relative to that of the AF data (in which rivaroxaban was administered with an evening meal). The bioavailability of the AF data was shown to be 1.12 (5.13% relative standard error) relative to that of the DVT data. The difference was contained within the bioequivalence limits of 80% to 125%,⁴ suggesting that the bioavailability of rivaroxaban under an evening meal condition and under a morning meal condition can be considered equivalent.

Simulation for Cross-Study PK Comparison

The simulated and estimated rivaroxaban PK parameters and steady-state exposures with a 20-mg once-daily dose regimen in both the DVT and AF data are graphically presented in Figure 3 and summarized in Table 4. Using the DVT model and the dosing, meal timing, and demographic information from the AF data, the plasma concentrations of rivaroxaban in the AF data were simulated. PK parameters and exposure measurements were estimated using the simulated data and then compared with the ones estimated using the observed concentrations in the AF data (Figure 3A, Table 4). Despite the difference in meal timing, demographics, and disease populations, the DVT model was able to predict the characteristics of observed AF data

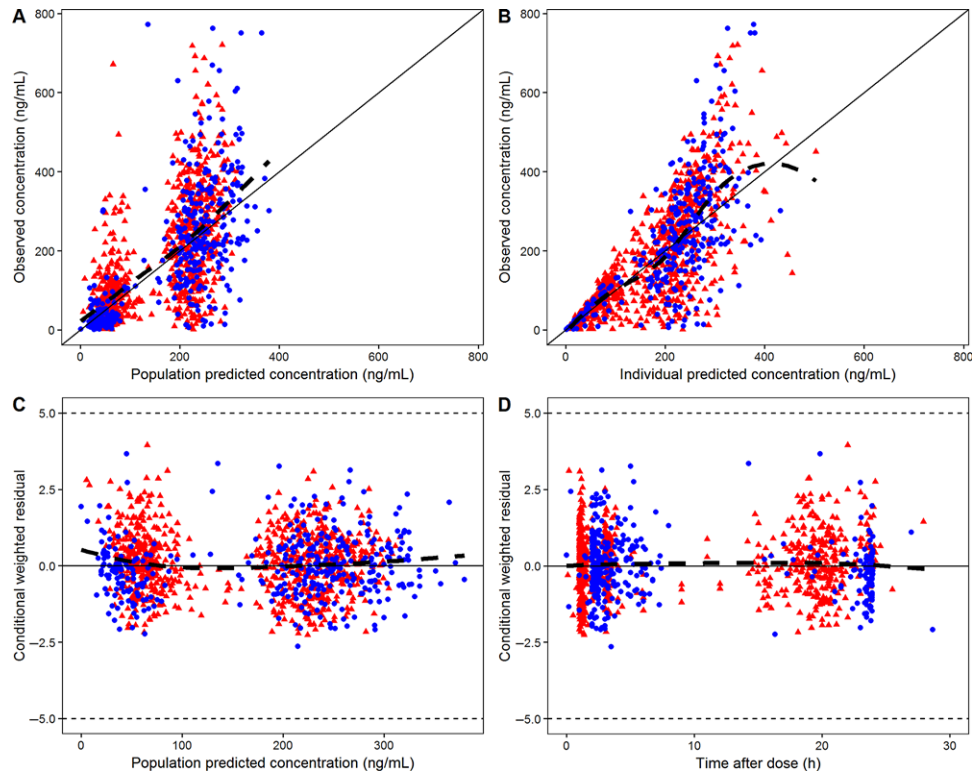


Figure 2. Diagnostic plots of the joint population PK model fitting to DVT data and AF data. (A) Observed rivaroxaban concentration versus population-predicted concentration. (B) Observed rivaroxaban concentration versus individual predicted concentration. (C) Conditional weight residual versus population-predicted concentration. (D) Conditional weight residual versus time after dose. Blue dots, DVT data; red triangles, AF data. Black dashed lines are locally smoothed trend lines going through data; black smooth lines are lines of identity (A and B) or lines of 0 (C and D); dotted lines are lines of ± 5 (C and D). PK, pharmacokinetic; DVT, deep vein thrombosis; AF, atrial fibrillation.

reasonably well. Similarly, simulated concentrations from the AF model were able to predict the characteristics of the observed DVT data reasonably well (Figure 3B, Table 4). The differences between the simulated

and estimated values were less than 20%, suggesting any differences between the PK of rivaroxaban administered with a morning meal and administered with an evening meal are unlikely to be clinically significant.

Table 3. Parameter Estimates From the Joint Population PK Model, Original DVT Model, and Original AF Model

Description	Estimate (RSE %)		
	Joint PK Model	DVT Model ¹²	AF Model ¹³
k_a , /h	0.982 (14.0)	1.23 (5.00)	1.16 (14.1)
Study on FI	1.12 (5.13)		
CL/F ^a L/h	6.31 (4.01)	7.16 (3.70)	6.10 (3.9)
IIV on CL/F ^a % CV	34.6 (11.8)	39.9 (7.60)	35.2 (14.3)
Age on CL/F ^a %	-0.0111 (17.7)	-0.0069 (14.6)	-0.011 (26.3)
SCr on CL, %	-0.244 (30.3)	-0.269 (18.2)	-0.194 (34.0)
V/F ^b L	70.3 (6.32)	68.7 (3.8)	79.7 (6.1)
IIV on V/F ^b % CV	15.5 (46.2)	28.8 (11.4)	17.6 (61.5)
LBM on V/F ^b %	0.109 (23.3)	0.0082 (17.8)	0.0118 (32.4)
Age on V/F ^b %	-0.00347 (63.4)	-0.0486 (20.8)	-0.00133 (188)
Proportional residual error, % CV	47.5 (5.22)	40.7 (3.2)	47.9 (6.2)

PK, pharmacokinetic; DVT, deep vein thrombosis; AF, atrial fibrillation; RSE, relative standard error (expressed as a percentage); k_a , first-order absorption rate; FI, relative bioavailability of AF versus DVT; CL/F, apparent clearance; IIV, interindividual variability; CV, coefficient of variation; SCr, serum creatinine concentration; V/F, apparent volume of distribution from the central compartment; LBM, lean body mass.

^aCL/F = $6.31 \times (1 - 0.0111 \times [\text{Age} - 65] - 0.244 \times [\text{SCr} - 1.05])/1.12$ [if DVT].

^bV/F = $70.3 \times (1 - 0.00347 \times [\text{Age} - 65] - 0.109 \times (\text{LBM} - 56.62))/1.12$ [if DVT].

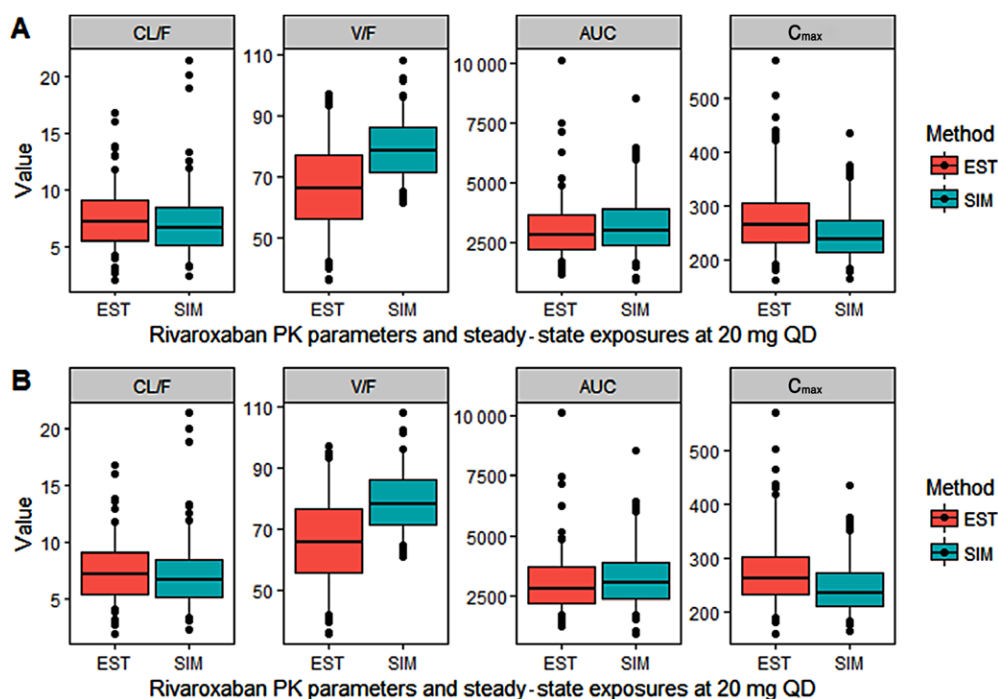


Figure 3. Box plot of estimated and simulated PK parameters and steady-state exposure of rivaroxaban at 20 mg once daily for (A) DVT data ($n = 124$) and (B) AF data ($n = 161$). PK, pharmacokinetic; DVT, deep vein thrombosis; AF, atrial fibrillation; CL/F, apparent clearance; V/F, apparent volume of distribution from central compartment; AUC, area under the plasma concentration–time curve; C_{max} , maximum drug concentration in plasma; QD, once daily; EST, estimated; SIM, simulated. Units for y axis: CL/F, L/h; V/F, L; AUC, ng·h/mL; C_{max} , ng/mL. Center, lower edge, and upper edge of the box denote median, 25th, and 75th percentiles; lower end and higher end of the vertical lines denote 5th and 95th percentiles.

Table 4. Estimated and Simulated PK Parameters of Rivaroxaban and Steady-State Exposures in DVT Data and AF Data

	20 mg Once Daily in DVT, $n = 124$ (Rivaroxaban Administered With Morning Meal)			20 mg Once Daily in AF, $n = 161$ (Rivaroxaban Administered With Evening Meal)		
	Estimated (Based on Observed Data), Median (5th and 95th Percentiles)	Predicted (Based on AF Model), Median (5th and 95th Percentiles)	Difference Between Estimated and Simulated, ^a %	Estimated (Based on Observed Data), Median (5th and 95th Percentiles)	Predicted Based on DVT Model), Median (5th and 95th Percentiles)	Difference Between Estimated and Simulated, ^a %
CL/F (L/h)	7.18 (4.12, 11.6)	6.63 (3.34, 11.9)	−7.66	6.19 (3.26, 10.3)	6.54 (3.54, 13.6)	5.65
V/F (h)	65.9 (42.4, 93.2)	78.4 (65, 96.1)	18.97	78.8 (61.6, 99.5)	68 (55.4, 84.1)	−13.71
AUC (ng·h/mL)	2790 (1720, 4850)	3010 (1680, 5980)	7.89	3150 (1860, 5390)	2940 (1390, 5300)	−6.67
C_{max} (ng/mL)	263 (190, 418)	237 (185, 353)	−9.89	238 (178, 329)	258 (192, 346)	8.40

PK, pharmacokinetic; DVT, deep vein thrombosis; AF, atrial fibrillation; CL/F, apparent clearance; AUC, area under the plasma concentration–time curve; V/F, apparent volume of distribution; C_{max} , maximum drug concentration in plasma.

^aCalculated as (median of simulated - median of estimated)/(median of estimated) \times 100.

Discussion

Based on the US prescribing guidelines,¹ 15- and 20-mg doses of rivaroxaban are recommended to be administered with food for the treatment of DVT or PE and for reducing the risk of recurrence of DVT and PE. In patients with AF, US prescribing guidelines recommend that both the 15- and 20-mg doses of rivaroxaban be administered with the evening meal. These recommendations are consistent with the administration of rivaroxaban in the pivotal phase

3 studies that were conducted as part of the clinical development program for rivaroxaban.^{8–11}

The current work was intended to evaluate the impact of food, in terms of both meal timing and content, on the PK of rivaroxaban at the approved dose regimen of 20 mg once daily for the DVT and AF populations (15 mg for subjects with $CrCl$ 30–49 mL/min). Through joint modeling of DVT and AF data, it was demonstrated that the model can describe the observed concentration–time data in both

Table 5. Summary of Phase I Studies Conducted in Healthy Volunteers With Rivaroxaban 20 mg^{3,5}

Dose	Meal Type	n	C _{max} , μg/L	AUC, μg·h/L
1 × 20 mg (whole tablet)	American breakfast: 42 g protein, ^a 67 g carbohydrates, ^a 63.5 g fat ^b ; 1051 total kcal	6	273	1990
1 × 20 mg (whole tablet)	Continental breakfast: 37 kcal protein (6%), 303 kcal carbohydrates (52%), 238 kcal fat (42%); 578 total kcal	4	275	2068
1 × 20 mg (whole tablet)	American breakfast: 42 g protein, ^a 67 g carbohydrates, ^a 63.5 g fat ^b ; 1051 total kcal	22	281	2048
20 mg (oral suspension)	American breakfast (42 g protein, ^a 67 g carbohydrates, ^a 63.5 g fat ^b ; 1051 total kcal)	17	226	1932
1 × 20 mg (whole tablet)	70 mL applesauce (~65 cal) and 130 mL water, followed by a liquid meal (750 cal) ^d	49	261 ^c	2279
1 × 20 mg (crushed tablet)	70 mL applesauce (~65 cal) and 130 mL water, followed by a liquid meal (750 cal) ^d	52	227	2141

C_{max}, maximum drug concentration in plasma; AUC, area under the plasma concentration–time curve; kcal, kilocalorie; cal, calorie.

^a 1 g = 4.2 kcal.

^b 1 g = 9.2 kcal.

^c n = 48.

^d 500 mL of Osmolite (1.5 cal/mL)

DVT and AF populations equally well. The relative bioavailability of the AF data compared with that of the DVT data was estimated to be 112% (standard error, 5.13%), which is well within the bioequivalence limits of 80% to 125%, suggesting equivalent PK of rivaroxaban under an evening-meal condition and a morning-meal condition.

Using the established population PK model that was previously built independently based on the clinical data obtained from the DVT and AF populations, model-based simulations showed that the characteristics of rivaroxaban PK at the 20-mg once-daily dose can be predicted across both the DVT and AF populations, despite the different underlying disease states, demographics, and meal intake times. These results suggested that, for a 20-mg once-daily regimen, the pharmacokinetics of rivaroxaban are consistent regardless of meal intake timing and content (ie, morning meal versus evening meal). This was the first attempt to compare the PK parameters of rivaroxaban, while focusing on the impact of food, using the PK data collected in a clinical trial setting. These findings are consistent with previous findings from the healthy volunteer clinical pharmacologic studies.^{3,5}

Four clinical pharmacology studies, designed in accordance with the Food-Effect Bioavailability and Fed Bioequivalence Studies Guidance for Industry⁴ from the FDA, evaluated the effects of food on the absorption of a 20-mg dose of rivaroxaban with different

meal statuses (fasted or fed) and meal types.^{3,5} The results of these studies are summarized in Table 5. The results from these pivotal food-effect studies supported the recommendation that the 15- and 20-mg doses of rivaroxaban be administered with food in the phase 2 studies assessing the use of rivaroxaban for DVT and phase 3 studies assessing the use of rivaroxaban for DVT, PE, and AF.

These previously conducted clinical pharmacologic studies allow for a greater understanding of the impact, or lack thereof, of different caloric intakes and meal contents (ie, standard high-calorie, high-fat breakfast³ based on the Guidance for Industry, a high-carbohydrate breakfast,¹⁴ or the consumption of applesauce followed by a low-calorie liquid meal⁵) on the PK of rivaroxaban in the context of this analysis. Results of this analysis of the varied meal timing and content and their potential impact on the PK parameters of rivaroxaban indicate that systemic exposure to a 20-mg dose of rivaroxaban was fairly consistent across meal types. Therefore, meal timing and content do not appear to impact the PK of rivaroxaban based on these trials.

In addition, there is an abundance of real-world data for rivaroxaban prescribed in a clinical setting. The results of the following real-world studies are generally consistent with those reported in pivotal phase 3 studies of rivaroxaban: XANTUS, a prospective observational study of rivaroxaban for stroke prevention in AF (n =

6784)¹⁵; XALIA, a prospective noninterventional study of rivaroxaban for DVT (n = 2505)¹⁶; REVISIT-US, a retrospective administrative claims database study of rivaroxaban for stroke prevention in nonvalvular AF (n = 11 411)¹⁷; and a postmarketing safety surveillance study to characterize major bleeding in patients with nonvalvular AF taking rivaroxaban (n = 27 467).¹⁸ It should be noted, however, that direct comparisons between these studies are not possible because of differences in study design and patient characteristics. The importance of this real-world data within the context of this food-effect analysis is that these studies represent patient data outside the more rigorous constraints of a clinical trial. Therefore, although the patients included in these real-world studies should have followed the prescribing directions regarding the proper dosing of rivaroxaban (eg, with food or with the evening meal, depending on the condition being treated), the content and timing of their meals would likely vary from patient to patient. The generally consistent safety and efficacy outcomes observed for rivaroxaban in these real-world studies, when indirectly compared with the pivotal phase 3 studies, helps to strengthen the position that meal type and timing do not play a significant role in successful treatment.

Conclusion

By comparing the predicted rivaroxaban PK parameters and steady-state exposures with those observed from the 20-mg once-daily dose regimen in the DVT and AF studies, it was concluded that the PK of rivaroxaban at this dose are not influenced by the timing or the content of the meal intake (ie, morning meal versus evening meal).

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Declaration of Conflicting Interests

L.Z., G.P., L.H., P.P., and P.N. are employees of Janssen Research & Development, LLC. K.T.M. is an employee of Janssen Scientific Affairs, LLC.

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