

# Bioequivalence Study of Capsules versus Film Tablets Containing Rivaroxaban in Healthy Caucasian Subjects under Fasting and Fed Conditions

Clinical Pharmacology  
 in Drug Development  
 2024, 13(3) 281–287  
 © 2023, The American College of  
 Clinical Pharmacology.  
 DOI: 10.1002/cpdd.1342

Gökçe Sözer<sup>1</sup>, Ahmet Inal<sup>2</sup>, Zafer Sezer<sup>2</sup>, Wolfgang Martin<sup>3</sup>, Ewald Ottmann<sup>3</sup>, Martin Reinsch<sup>4</sup>, and Selma Alime Kuru<sup>5</sup>

## Abstract

The bioequivalence (BE) of orally administered capsules versus film tablets containing 20 and 10 mg of rivaroxaban was assessed in 2 single-dose, open-label, randomized 2-way crossover trials with a washout period of at least 1 week. The study for the 10 mg strength was conducted under fasting conditions (n = 68) and the study for the 20 mg strength under fed conditions (n = 52). Blood samples were collected over a 36-hour period and concentrations were assayed using a liquid chromatography tandem mass spectrometry method. Pharmacokinetic (PK) evaluation was performed with the program Phoenix WinNonlin, for non-compartmental assessment of data.

After administration of 10 mg rivaroxaban under fasting conditions, mean Area Under the time - concentration Curve until the last blood sampling point ( $AUC_t$ ), Area Under the time - concentration Curve until infinity ( $AUC_{\infty}$ ), and maximum plasma concentration ( $C_{max}$ ) were comparable (972 ng/mL\*h, 1048 ng/mL\*h, and 111 ng/mL, respectively, for the test and 1013 ng/mL\*h, 1070 ng/mL\*h and 130 ng/mL, respectively, for the reference formulation). Mean  $AUC_t$ ,  $AUC_{\infty}$ , and  $C_{max}$  were also comparable under fed conditions after administration of 20 mg rivaroxaban (2145 ng/mL\*h, 2198 ng/mL\*h and 275 ng/mL, respectively, for the test and 1856 ng/mL\*h, 1916 ng/mL\*h and 240 ng/mL, respectively, for the reference formulation). The 90% confidence intervals for all PK parameters were within the acceptance range of 80%-125%, suggesting BE between the generic product and the innovator product in healthy Caucasian male subjects. A clinically relevant difference in the tolerability and safety of the treatments was not detected. Study results indicated that the capsule formulations were bioequivalent with the film tablet formulations.

## Keywords

bioequivalence, pharmacokinetics, rivaroxaban, capsule, film tablet, variation

Factor Xa is a coagulation factor that operates in the blood coagulation system and is critical for the cleavage of prothrombin in order to form thrombin, which finally causes coagulation.<sup>1,2</sup> Rivaroxaban acts dose dependently and inhibits free as well as prothrombinase-bound and clot-associated factor Xa.<sup>3</sup> In other words, rivaroxaban prevents thrombin formation via both the intrinsic and extrinsic pathways.<sup>4</sup> Also, in vitro studies performed in platelet-poor and platelet-rich plasma have demonstrated rivaroxaban to prolong the initiation phase of thrombin generation and to reduce the thrombin burst produced in the propagation phase.<sup>3</sup> In human plasma, rivaroxaban effectively and dose dependently inhibits factor Xa activity and prolongs both prothrombin time (PT) and activated partial thromboplastin time (aPTT).<sup>5</sup>

Rivaroxaban was the first authorized direct factor Xa inhibitor used in adult patients for the prophylaxis

<sup>1</sup> Sanovel İlaç Sanayi ve Ticaret A.Ş., İstanbul, Türkiye

<sup>2</sup> Hakan Çetinsaya Good Clinical Practise Centre (IKUM), Erciyes University and Department of Medical Pharmacology, Faculty of Medicine, Erciyes University, Kayseri, Türkiye

<sup>3</sup> Pharmakin Consulting Services UG, Neu-Ulm, Germany

<sup>4</sup> Analytisches Zentrum Biopharm GmbH, Berlin, Germany

<sup>5</sup> IDEAL Biyolojik Ürünler ve İlaç Danışmanlık Eğitim Ltd. Şti, Ankara, Türkiye

Submitted for publication 10 August 2023; accepted 22 October 2023.

## Corresponding Author:

Gokce Sozer, Büyükdere Caddesi, Esentepe Mahallesi Bahar Sokak No: 13, Kat: 10 (River Plaza) – Şişli, İstanbul, Türkiye  
 (e-mail: gokcesozer@sanovel.com.tr)

of venous thromboembolism after elective hip or knee arthroplasty. Rivaroxaban was later on also approved for prevention of stroke and systemic embolism in adult non-valvular atrial fibrillation patients with 1 or more risk factors (such as congestive heart failure, hypertension, age  $\geq$  75 years, diabetes mellitus, prior stroke, or transient ischemic attack), and the treatment and prevention of recurrence of deep vein thrombosis and pulmonary embolism in adults<sup>6</sup>.

Hard capsule formulations are generally known to have fewer excipients. Additionally, they are less likely to have an unpleasant taste or odor compared with soft capsules or tablets and are more tamper-resistant. Hard capsules are often not easy to split in half or crush, like tablets. To increase patient compliance, we developed our products containing rivaroxaban as a hard capsule formulation.

Bioavailability of rivaroxaban 10-mg tablets in terms of rate [maximum plasma concentration ( $C_{\max}$ )] and extent [area under the time - concentration curve (AUC)] were shown to be irrespective of food intake whereas the total bioavailability decreased for 66% under fasting conditions after oral administration of the 20 mg strength and the mean AUC increased by 39%.<sup>7,8</sup> Therefore, higher strengths are recommended to be taken with food to achieve higher bioavailability.<sup>9</sup> It was shown that neither meal timing nor meal content appeared to have relevant different effects on bioavailability.<sup>7,10</sup>

Since there is a different food effect resulting in different administration recommendations for the lower (2.5 and 10 mg) and higher (15 and 20 mg) strengths, 2 bioequivalence (BE) studies were performed: 1 study under fasting conditions with the 10 mg strength and 1 study under fed conditions with the 20 mg strength to represent both extreme situations. In these studies, we aimed to investigate the pharmacokinetic (PK) properties of rivaroxaban among healthy male Caucasian subjects and to evaluate the BE of capsules versus film tablets. For a drug to be considered bioequivalent to the reference drug, the 90% confidence interval (CI) of the test/reference (T/R) for AUC and  $C_{\max}$  should be within 80%-125%.

## Methods

### Study Design

Both studies were designed as randomized, open-label, 2-period, 2-sequence, cross-over studies. Under study 1, 52 healthy male Caucasian subjects were dosed under fed conditions, investigating the BE of rivaroxaban in a 20 mg strength. Study 2 compared the BE of the 10 mg strength of the test product with the reference product in 68 healthy male Caucasian subjects, under fasting conditions. In each study, subjects received both the

test and the reference products in 2 different treatment regimens (sequence TR or RT) with at least a 1-week washout period and remained at the clinical facility for 1 night in each period, from the day before dosing until 12 hours post administration. Blood sampling at 24 and 36 hours post-administration was performed ambulatory.

The clinical part was not blinded since no risks of bias is expected in PK studies. Knowledge of the administered product would not influence the PK assessments. Only the researcher involved in the analytical phase was blinded until the analytical part was completed.

Screening for eligibility included a physical examination, assessment of medical-surgical history as well as lifestyle and habits, registration of birth date, ethnic group and gender, determination of height, weight and body mass index (BMI), measurement of body temperature, blood pressure and heart rate after 5 minutes supine rest, and registration of a 12-lead electrocardiogram (ECG). Additionally, laboratory blood investigation tests (hemoglobin, hematocrit, leukocytes, erythrocytes, platelet count, PT, aPTT, sodium, potassium, calcium, chloride, aspartate transaminase, alanine transaminase, gamma glutamyl transferase, alkaline phosphatase, creatinine, creatinine clearance, total protein, total bilirubin, blood glucose, blood urea nitrogen, uric acid) and urine evaluation [pH, protein, glucose, ketones, blood (erythrocytes), leukocytes, bilirubin, urobilinogen, nitrites, specific gravity, sediment] inclusive of drug screen in urine (qualitative determination of amphetamines, cannabinoids, benzodiazepines, cocaine, opioids, barbiturates) were performed. Screening procedures were affected within 9 days prior to the subjects' first dosing days in both studies. Administration of any prescribed systemic or topical medication within 2 weeks and over-the-counter medication (including herbal remedies) within 1 week prior to the start of the study was determined as an exclusion criterion. Concomitant medication (including herbal remedies) was generally not allowed for the duration of the trial. If concomitant medication was considered to be necessary for the subject's welfare it could be given at the discretion of the investigator. The subjects had to inform the investigator about any intake of other drugs in the course of the trial. For the treatment of ordinary pain (eg, headache), analgesics (paracetamol) was allowed to be given if required.

Male subjects aged between 18 and 55 years within a normal BMI range (18.5-30 kg/m<sup>2</sup>) and who had signed the informed consent were enrolled in both studies. Subjects with known contraindications or hypersensitivities to rivaroxaban or similar products, chronic gastrointestinal problems, liver dysfunction, clinically significant hematological diseases, renal insufficiency, and positive test results for hepatitis B surface antigen,

hepatitis C virus, and/or human immunodeficiency virus were excluded.

These studies were carried out in accordance with the Declaration of Helsinki (Fortaleza, Brazil, October 2013). The study protocol, the informed consent form, case report form (CRF), and related other documentation was reviewed and approved by an independent Ethics Committee, Ethics Committee for Bioavailability-Bioequivalence Trials of Erciyes University and the Turkish Medicines and Medical Devices Agency of MoH. Written informed consent was obtained from every subject prior to the start of any trial-related activities. The investigator retained 1 copy of the consent forms and subjects were given another copy of the forms.

### Study Products

The test products in study 1 were Rivaroxaban 20 mg Capsules (batch no: 1710A002, exp. date: 02.2019) and the test products in study 2 were Rivaroxaban 10 mg Capsules (batch no: 1708A002, exp. date: 02.2019), both manufactured by Sanovel İlaç Sanayi ve Ticaret A.S., at their facilities in Silivri (Istanbul, Türkiye) under Good Manufacturing Practices. The reference preparations were the innovator products (Xarelto 20 mg Film Tablets and Xarelto 10 mg Film Tablets; Bayer Pharma AG) purchased from the German Market.

### Treatment Phase and Blood Sampling

Subjects attended the clinical facility, Erciyes University Hakan Çetinsaya İyi Klinik Uygulama ve Araştırma Merkezi, İKUM (Centre for GCP; Kayseri, Türkiye), the day before drug administration. After hospitalization, subjects received an evening snack (total caloric value ~600 kcal) at about 7:30 pm and had to finish until 9:00 pm.

In study 1, following an overnight fasting period of at least 10 hours and after having started consumption of a high-fat breakfast 30 minutes before dosing, either test or reference preparation corresponding to a dose of 1×20 mg rivaroxaban each was administered orally together with 240 mL of tap water.

In study 2, following an overnight fasting period of at least 10 hours, either test or reference preparation corresponding to a dose of 1×10 mg rivaroxaban each was administered orally together with 240 mL of tap water under fasting conditions.

For investigation of rivaroxaban PKs, blood samples were withdrawn prior to administration 0 (pre-dose) and at 0.25, 0.50, 1, 1.50, 2, 2.50, 3, 3.50, 4, 4.50, 5, 6, 9, 12, 24, and 36 hours postdose in both studies. The date and time at which each sample was taken were recorded. Lunch and dinner were provided 4 and 10 hours after drug administration, respectively. The amounts of

food and water intake and physical activity for each individual subject were standardized during the sampling days. Xanthine-containing food or beverages and fruit juices were not allowed during the stay in the clinical facility.

At pre-determined time points, ~7 mL of blood was taken from a cubital or forearm vein by either an indwelling catheter or individual venepuncture into tubes with K<sub>2</sub>EDTA as anticoagulating agent. After sampling, blood samples were transferred into a mini refrigerator (temperature adjusted to 4 ± 2°C) for a maximum period of 20 minutes. The blood samples were centrifuged (3000 rpm, 4–7°C, 10 minutes) and the supernatant plasma from each sample was given within 20 minutes into 3.5-mL labelled polypropylene storage tubes (2 tubes per sample, at least 1.5 mL per tube). Afterwards tubes were capped, transferred to a deep freezer (<-70°C) and kept frozen until dispatch to the analytical facility at Analytisches Zentrum Biopharm GmbH (Berlin, Germany).

### Bioanalytical Method

A high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) method was validated for rivaroxaban in August 2017 to show the selectivity, intra-assay and inter-assay precision and accuracy, lower limit of quantification, dilution integrity, carry over, recovery, matrix effect, linearity of the standard curve from 2.00 to 50,000 ng/mL in plasma and stability data (bench top, freeze thaw, auto sampler, extract stability, and long term stability). The results showed that it is possible to quantify rivaroxaban in plasma samples with sufficient accuracy, precision, specificity, and sensitivity. Furthermore, 98% of incurred sample reanalysis samples passed acceptance criteria during the measurement of study samples.

This validated HPLC-MS/MS method was used to determine rivaroxaban in plasma samples of both studies. Rivaroxaban and the internal standard (IS) (rivaroxaban-d<sub>4</sub>) were separated under isocratic conditions with methanol and formic acid in water using a C18 HPLC column. Ionization and detection of analyte and IS were carried out on a triple quadrupole mass spectrometer, ABSCIEXAPI-4000 (Darmstadt, Germany), equipped with electrospray ionization (TIS interface of the API 4000) and operated in the positive ion mode. Quantitation was performed using the multiple reaction monitoring mode to monitor parent-product ion (m/z) transitions 435.997→144,700 for rivaroxaban and 440.100→144,700 for rivaroxaban-d<sub>4</sub>.

All chromatographic data were collected using Analyst (version 1.5.2) chromatographic software. The method and the sequence file were constructed and downloaded prior to the injection of the first sample. For each assay day, a standard curve was constructed by

plotting peak area ratios for analyte/internal standard versus the respective standard concentration. Sample concentrations were determined mathematically by comparing the peak area ratios in the sample to the weighted ( $1/x^2$ ) regression equation obtained from the standard data. The calibration function and the calculation of sample concentration were performed using validated Software dbLabCal (version V3).

### PK Evaluation and Statistics

Individual PK parameters Area Under the time - concentration Curve until the last blood sampling point ( $AUC_t$ ), Area Under the time - concentration Curve until infinity ( $AUC_\infty$ ), Time to maximum plasma concentration ( $C_{max}$ ,  $t_{max}$ ) and half-life ( $t_{1/2}$ ) were determined. Target variables were defined as the intra-individual bioavailability ratios after single doses of the test over the reference preparation in the measures  $AUC_t$  and  $C_{max}$  for rivaroxaban. Bioequivalence was to be stated if acceptance criteria (80.00%-125.00%) of 90% CI for T versus R were met for  $AUC_t$  and  $C_{max}$  of rivaroxaban. Further PK measures after single dose administration ( $AUC_\infty$ ,  $t_{max}$ ,  $t_{1/2}$ ) were also determined for rivaroxaban.

PK evaluation was performed with the program Phoenix WinNonlin for non-compartmental assessment of data. For  $t_{max}$ , a non-parametric evaluation using 2 one-sided Wilcoxon tests comparing differences was applied.

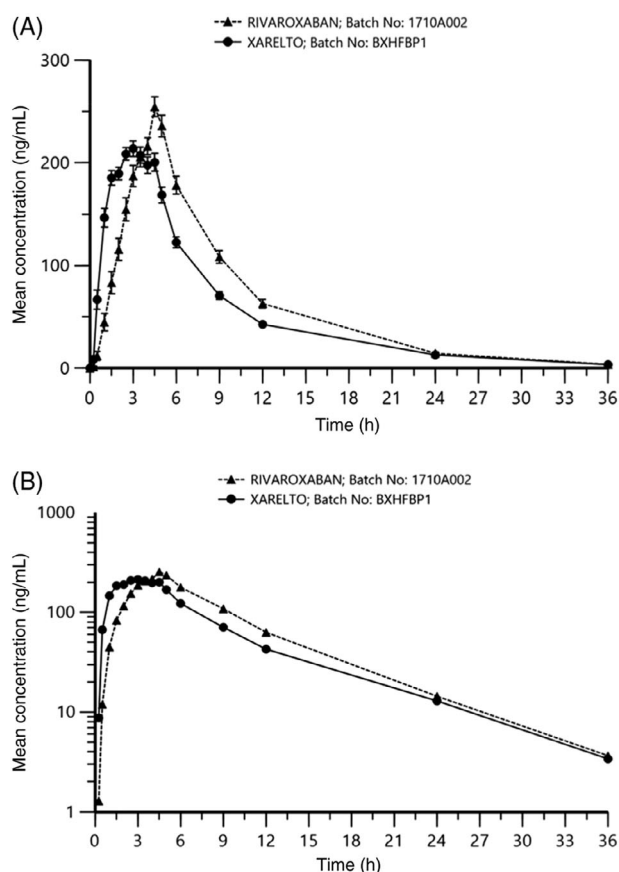
### Safety Evaluation

All adverse events (AEs) either spontaneously reported by the participating subject or observed by the investigator, during regularly performed questionings on admission to the clinical unit prior to both study periods and at study times 0 (within 60 minutes before dosing), 1, 6, 12, 24, and 36 hours post-administration, were recorded on an AE information sheet in the subject's CRF. In addition, blood pressure (systolic, diastolic) and heart rate were measured during entry and final examinations. One ECG was recorded for each subject during entry and final examinations. Results of individual blood pressure (systolic, diastolic) and heart rate measurements were recorded into the CRF's of each subject. PT, aPTT, and calculation of creatinine clearance were also performed during entry and final examination for safety purposes.

## Results

### Study 1

**PK Results.** A total of 66 Caucasian male subjects were screened by physical examination and clinical laboratory tests. Fifty-two healthy male subjects were enrolled in the study. Fifty-two subjects, between 21 and 50 years of age and with a BMI range of 18.9-29.9  $kg/m^2$ , completed the study regularly according to



**Figure 1.** Mean concentrations ( $\pm$  standard error of the mean (sem)) of rivaroxaban in plasma after administration of different (T and R) 20-mg rivaroxaban-containing preparations under fed conditions: linear (A) and loglinear (B) plots,  $n = 52$ .

the study protocol so that plasma samples of 52 completed cases for each treatment were available for the analysis of rivaroxaban concentrations. A summary of the demographic data can be seen in Table 3.

Rivaroxaban PK parameters  $AUC_t$ ,  $AUC_\infty$ , and  $C_{max}$  were similar between the tablet and capsules (Tables 1 and 2). Mean rivaroxaban plasma concentration-time profiles stratified by treatments are presented in Figure 1.

For evaluation of BE between test preparation and reference preparation, the 90% CI (ANOVA; 2 one-sided t-tests) for the T/R ratios of geometric means of the PK target variables  $AUC_t$  and  $C_{max}$  were calculated based on the assumption of a lognormal distribution of individual data. The other PK parameters  $AUC_\infty$  and  $t_{max}$  served as supportive data.  $AUC_\infty$  was evaluated in the same way as  $AUC_t$ , applying a multiplicative model;  $t_{max}$  was subjected to non-parametric analysis (90% CI of 2 one-sided Wilcoxon tests). The observed 90% CIs, including pertaining point estimators (ratios T/R of geometric means), are shown in Table 2.

**Safety Results.** In the course of the study, no treatment emergent AEs occurred in 52 enrolled subjects.

**Table 1.** PK Parameters (Arithmetic Mean  $\pm$  Standard Deviation) of 20 mg Rivaroxaban under Fed Conditions; n = 52 Subjects

Treatment	AUC <sub>t</sub> (ng/mL*h)	AUC <sub>∞</sub> (ng/mL*h)	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (hour)	t <sub>1/2</sub> (λ <sub>z</sub> ) (hour)
Test product	2145 $\pm$ 570	2198 $\pm$ 572	275 $\pm$ 68	4.3 $\pm$ 1.1	5.6 $\pm$ 1.5
Reference product	1856 $\pm$ 519	1916 $\pm$ 529	240 $\pm$ 47	2.6 $\pm$ 1.3	6.4 $\pm$ 1.6

**Table 2.** Statistical Assessment of Bioequivalence Comparing T and R: Containing 20 mg Rivaroxaban, n = 52 and Containing 10 mg Rivaroxaban, n = 68

PK parameter: (ANOVA; 2 one-sided t-tests)	90% CI		Point estimators (ratios T/R of geometric means)		Intra-subject coefficient of variance (CV)	
	20 mg	10 mg	20 mg	10 mg	20 mg	10 mg
AUC <sub>t</sub>	110.7%-122.5%	92.4%-100.3%	116.5%	96.3%	15.5%	14.5%
C <sub>max</sub>	106.8%-120.3%	80.7%-90.9%	113.4%	85.6%	18.3%	21.0%
AUC <sub>∞</sub>	110.3%-121.1%	94.6%-102.1%	115.6%	98.3%	14.4%	13.3%

**Table 3.** Summary of Demographic Data

Parameter	Study 1				Study 2			
	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m <sup>2</sup> )	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m <sup>2</sup> )
Mean value	34.0	76.2	174.6	25.0	34.6	73.9	172.2	24.9
Standard deviation	8.5	11.3	6.4	3.0	7.9	10.2	6.7	3.1
CV (%)	25.1	14.9	3.7	11.9	22.8	13.7	3.9	12.4
Minimum	21	55.1	162	18.9	21	49.5	152	19.1
Maximum	50	99.0	186	29.9	52	90.0	187	29.9
Number	52	52	52	52	68	68	68	68

Also, no severe or serious AEs were recorded. All laboratory safety tests and physical examinations, including blood pressure and heart rate measurements performed at study termination, did not show clinically relevant abnormalities or changes compared to the entry examination. In addition, ECGs recorded at final examination and special tests (PT, aPTT, creatinine clearance) did not show changes or signs of abnormality compared to the entry examination, with 1 ECG exception (sinus tachycardia, judged to be of no clinical relevance).

## Study 2

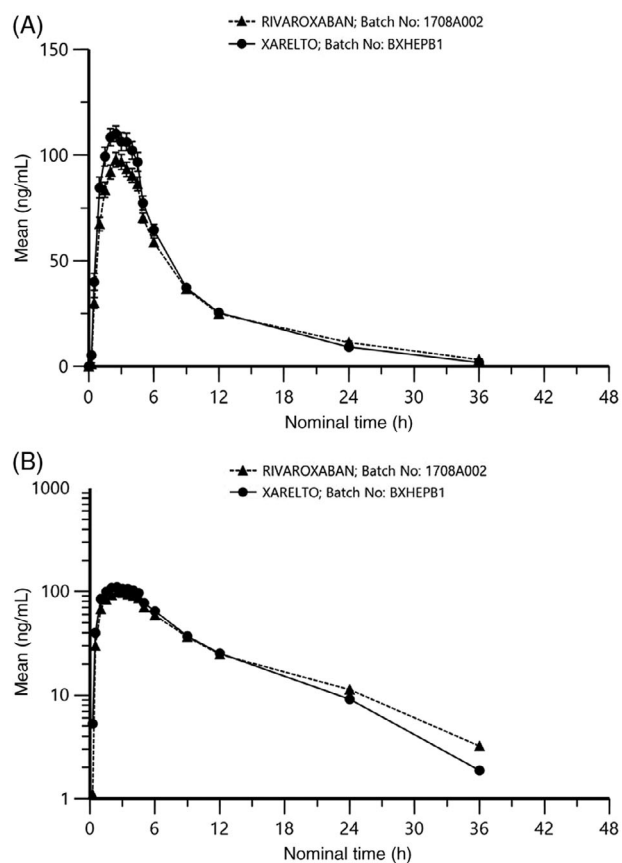
**PK Results.** Ninety-one male Caucasian subjects were screened by physical examination and clinical laboratory tests. Sixty-eight healthy male subjects were enrolled in the study. All 68 subjects, between 21 and 52 years and with a BMI range of 19.9-29.9 kg/m<sup>2</sup>, completed the study regularly according to the study protocol so that plasma samples of 68 completed cases for each treatment were available for the analysis of rivaroxaban concentrations. A summary of the demographic data can be seen in Table 3.

Rivaroxaban PK parameters AUC<sub>t</sub>, AUC<sub>∞</sub>, and C<sub>max</sub> were similar between the tablet and capsules (Tables 2 and 4). Mean rivaroxaban plasma concentration-time profiles stratified by treatments are presented in Figure 2.

**Safety Results.** In the course of the study, 5 treatment-emergent AEs occurred in 5 out of 68 enrolled subjects. Two treatment-emergent AEs (headache) were of moderate intensity, occurring in period II after the test preparation and in period I after the reference preparation. The AE observed after the reference preparation was treated with 500 mg paracetamol given 9 hours 13 minutes postdose. Three further treatment-emergent AEs (1  $\times$  orthostatic hypotension, 1  $\times$  itching and 1  $\times$  abdominal pain) were of mild intensity. All occurred in period I, itching after the reference preparation and orthostatic hypotension as well as abdominal pain after the test preparation. Apart from orthostatic hypotension with drug relationship judged to be “unlikely,” all other 4 treatment-emergent AEs were judged to be “possible” drug-related. All treatment-emergent AEs recovered without sequelae. No severe or serious AEs were recorded.

**Table 4.** PK Parameters (Arithmetic Mean  $\pm$  Standard Deviation) of 10 mg Rivaroxaban under Fasting Conditions, n = 68 Subjects

Treatment	AUC <sub>t</sub> (ng/mL*h)	AUC <sub>∞</sub> (ng/mL*h)	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (hour)	t <sub>1/2</sub> (λ <sub>z</sub> ) (hour)
Test product	972 $\pm$ 223	1048 $\pm$ 226	111 $\pm$ 28	2.5 $\pm$ 1	9.0 $\pm$ 3.7
Reference product	1013 $\pm$ 245	1070 $\pm$ 241	130 $\pm$ 36	2.3 $\pm$ 1	7.3 $\pm$ 2.7

**Figure 2.** Mean concentrations ( $\pm$  standard error of the mean (sem)) of rivaroxaban in plasma after administration of different (T and R) 10-mg rivaroxaban-containing preparations under fasting conditions: linear (A) and loglinear (B) plots, n = 68.

## Discussion

The capsule was manufactured using the dry mixing method as the active ingredient was determined by its fluidity. Excipients, which are generally preferred in capsules, were used in the development of the formulation. The amounts of excipients were determined to obtain an optimum capsule formulation. The general approach was followed for solid dosage forms using equipment that is frequently used as a production method and did not require special production equipment. Since there is a dose proportionality between the rivaroxaban 10-mg capsule and rivaroxaban 20-mg capsule formulations, pharmaceutical development was carried out with the 20-mg dose. When the final

formulation was established, a large-scale trial was conducted for 10 mg.

Due to the differences in food effect between strengths resulting in different food recommendations for the lower (2.5 and 10 mg) and higher (15 and 20 mg) strengths, 2 studies were performed. The aim of the present trials was to investigate the BE between test and reference preparations all containing rivaroxaban. These clinical trials were conducted with the aim of investigating whether any differences concerning the rate and extent of absorption exist between the capsule and film tablet preparations. The reference drugs in the present studies are already registered and commercially available in Germany. For the purpose of registration, the efficacy and safety of these drugs have been proved in clinical trials. These drugs therefore served as reference and basis for comparison with the test products manufactured by Sanovel İlaç Sanayi ve Ticaret A.S., Türkiye. Study results were well comparable with literature data. After administration of a single oral dose of 10 mg of rivaroxaban under fasting conditions AUC<sub>t</sub>, C<sub>max</sub>, t<sub>max</sub>, and t<sub>1/2</sub> values were seen to be about 1000 ng/mL\*h, 130 ng/mL, 2.5 hours, and 7-10 hours, respectively. The same PK parameters after administration of a single oral dose of 20 mg rivaroxaban under fed conditions were 2000 ng/mL\*h, 290 ng/mL, 3 hours, and 5-9 hours, respectively. All study results confirmed the literature data and were essentially in the mentioned ranges.<sup>9,11,12</sup> Literature data also report a delayed t<sub>1/2</sub> in elderly subjects, which explains some differences between the results.<sup>9</sup>

In summary, 52 subjects completed the study under fed conditions, and all 68 volunteers finished the fasting study. No significant difference was seen in the t<sub>max</sub> value for the test product or reference product within the fasting study or within the study under fed conditions. After the 7-day washout period no rivaroxaban was detected in the predose samples, which showed the absence of a residual effect of the previous casting on the subsequent cycle. The absolute bioavailability of rivaroxaban is dose dependent.<sup>7,8</sup> In the case of the 2.5- and 10-mg doses, it is estimated to be 80%-100% without being affected by food. Rivaroxaban 2.5- and 10-mg tablets can be taken with or without food. Co-administration of rivaroxaban with food increases the bioavailability of the 20-mg dose (AUC and C<sub>max</sub>

values increased by 39% and 76%, respectively). Thus, rivaroxaban 15- and 20-mg tablets should be taken with food.<sup>7,8</sup>

## Conclusion

The BE between test and reference products of both strengths was demonstrated in male Caucasian subjects after administration of single oral doses under fed and fasting conditions.

## Acknowledgments

The authors would like to acknowledge the effort of the below in alphabetic (surname) order listed study personnel for their contribution to this work.

## Author Contributions

Sanovel (sponsor) study team: Ali Türkyılmaz, Sibel Zenginler, Erkin Öztürk. IKUM (clinical center): Meltem Afşar, Murat Altinkılıç, Rifat Baykan, Özlem Bulmuş, Mevlüt Ceylan, Ali Çat, Nuray Doğan, Mustafa Eroğlu, Büşra Karaca, Çiğdem Karabacak, Hüseyin Karakaya, Mustafa Karaşen, Vedat Kenger, Demet Kibar, Mümtaz Mazicioğlu, Sabahattin Muhtaroglu, Ayfer Şahin, Çiğdem Şahin Gençtürk, Özgür Soydan, Ömer Tınaz. AZB (analytical center): Xiaodan Du, Anne Querner. Pharmakin (statistical and reporting center): Renate Martin.

## Conflicts of Interest

All study partners were paid by Sanovel İlaç Sanayi ve Ticaret A.S., Türkiye for their efforts in realizing the study and the preparation of the manuscript, on a company basis. No author was personally paid. Gökçe Sözer, Ahmet Inal, Zafer Sezer, Wolfgang Martin, Ewald Ottmann, Martin Reinsch, and Selma Alime Koru declare that they have no other conflicts of interest.

## Funding

This study and manuscript was funded by Sanovel İlaç Sanayi ve Ticaret A.S., Türkiye.

## References

1. Ansell J. Factor Xa or thrombin: is factor Xa a better target? *J Thromb Haemost.* 2007;5 (suppl 1):60-64.
2. Furie B, Furie BC. Mechanisms of thrombus formation. *N Engl J Med.* 2008;359(9):938-949.
3. Zdovc J, Petre M, Pišlar M, et al. Downregulation of ABCB1 gene in patients with total hip or knee arthroplasty influences pharmacokinetics of rivaroxaban: a population pharmacokinetic-pharmacodynamic study. *Eur J Clin Pharmacol.* 2019;75(6):817-824.
4. Perzborn E, Roehrig S, Straub A, et al. Rivaroxaban: a new oral factor Xa inhibitor. *Arterioscler Thromb Vasc Biol.* 2010;30(3):376-381.
5. Graff J, von Hentig N, Misselwitz F, et al. Effects of the oral, direct factor xa inhibitor rivaroxaban on platelet-induced thrombin generation and prothrombinase activity. *J Clin Pharmacol.* 2007;47(11):1398-1407.
6. Perzborn E, Strassburger J, Wilmen A, et al. In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939 – an oral, direct Factor Xa inhibitor. *J Thromb Haemost.* 2005;3(3):514-521.
7. Kubitzka D, Becka M, Zuehlsdorf M, et al. Effect of food, an antacid, and the H2 antagonist ranitidine on the absorption of BAY 59-7939 (rivaroxaban), an oral, direct factor Xa inhibitor, in healthy subjects. *J Clin Pharmacol.* 2006;46(5):549-558.
8. Stampfuss J, Kubitzka D, Becka M, et al. The effect of food on the absorption and pharmacokinetics of rivaroxaban. *Int J Clin Pharmacol Ther.* 2013;51:549–561
9. Mueck W, Stampfuss J, Kubitzka D, et al. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. *Clin Pharmacokinet.* 2014;53(1):1-16.
10. Zhang L, Peters G, Haskell L, et al. A cross-study analysis evaluating the effects of food on the pharmacokinetics of rivaroxaban in clinical studies. *J Clin Pharmacol.* 2017;57(12):1607-1615.
11. Ding S, Wang L, Xie L, et al. Bioequivalence study of 2 formulations of rivaroxaban, a narrow-therapeutic-index drug, in healthy Chinese subjects under fasting and fed conditions. *Clin Pharmacol Drug Dev.* 2020;9(3):346-352.
12. Zhao X, Sun P, Zhou Y, et al. Safety, pharmacokinetics and pharmacodynamics of single/multiple doses of the oral, direct Factor Xa inhibitor rivaroxaban in healthy Chinese subjects. *Br J Clin Pharmacol.* 2009;68(1):77-88.