

Pharmacokinetics and Bioequivalence of Two Rivaroxaban Oral Formulations: A Randomized, Four-Period Crossover Study under Fasting and Fed Conditions

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Abstract

Objective: This study aimed to compare the rate and extent of absorption of two oral rivaroxaban 20 mg formulations: Asarap® (Laboratorios Leti S.A.V.) as the test (T) and Xarelto® (Bayer A.G.) as the reference (R), in a randomized, single-dose, four-period, two-sequence crossover design. **Methods:** Healthy subjects received a single oral dose of T or R under fasting (n = 36) and fed (n = 40) conditions. A 5-day washout was applied between periods, for a total study duration of 19 days. Blood samples were collected pre-dose and up to 48 hours post-dose. Plasma rivaroxaban concentrations were determined using a validated LC-MS/MS method. Primary pharmacokinetic parameters included C_{max} , AUC_{0-t} , and AUC_{0-inf} . Statistical analyses were performed using SAS® version 9.4. **Results:** Under fasting conditions, Geometric Mean Ratios (GMRs) (90% CI) were: C_{max} 107.70% (99.85 - 116.17), AUC_{0-t} 109.35% (102.52 - 116.63), and AUC_{0-inf} 108.85% (102.48 - 115.60). Under fed conditions, GMRs were: C_{max} 102.19% (97.87 - 106.70), AUC_{0-t} 98.69% (95.37 - 102.13), and AUC_{0-inf} 98.87% (95.67 - 102.18). All parameters met the predefined bioequivalence range (80% - 125%). No adverse events were reported. **Conclusion:** The test and reference formulations were bioequivalent under both fasting and fed conditions.

Keywords

Pharmacokinetic, Rivaroxaban, Bioequivalence, Anticoagulant

1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide. An es-

estimated 19.8 million people died from CVD in 2022, representing approximately 32% of all global deaths, with 85% attributed to heart attacks and strokes. The World Health Organization (WHO) projects that annual deaths from CVD will reach 23.6 million by 2030 [1].

Thrombosis is the underlying cause of most heart attacks, strokes, and venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE). The estimated global annual incidence of VTE ranges from approximately 115 to 269 cases per 100,000 population [1]-[3]. Overall, thrombosis is responsible for approximately one in four deaths related to CVD [4]-[8].

Rivaroxaban is an oral, direct-acting anticoagulant (DOAC) that selectively and reversibly binds to the active site of activated factor X (Xa). This interaction rapidly and competitively inhibits factor Xa, thereby preventing thrombin generation and its downstream effects [9] [10].

Rivaroxaban is classified as a Biopharmaceutics Classification System (BCS) Class II drug [10] and exhibits a dose-dependent food effect [11]. Lower-dose tablets (2.5, 5, and 10 mg) can be administered with or without food [4] [10]-[12]. In contrast, higher-dose tablets (15 and 20 mg) should be taken with food to enhance oral absorption and systemic availability. This recommendation is based on observations of approximately a two-fold increase in solubility under fed conditions [10]-[13].

Rivaroxaban is rapidly absorbed, reaching maximum plasma concentration (C_{max}) within 2 - 4 hours after a single oral dose. Its oral bioavailability (BA) is high—approaching 100% under both fasting and fed conditions—for the 2.5 mg, 5 mg, and 10 mg doses. However, for the 20 mg dose, bioavailability is reduced to approximately 66% under fasting conditions [4] [9]-[13].

At higher doses (15 mg and 20 mg), rivaroxaban demonstrates dose proportionality when administered under fed conditions. The increased solubility observed in the fed state is attributed to the lipid components of the gastrointestinal environment, which enhance drug solubilization and result in improved bioavailability of 80% or greater [4] [10]-[13].

Rivaroxaban is metabolized primarily via cytochrome P450 enzymes CYP3A4 and CYP2J2, as well as through CYP-independent pathways. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds represent the primary pathways of rivaroxaban biotransformation. Overall, pharmacokinetic (PK) variability is moderate, with within-subject variability (coefficient of variation, CV%) of approximately 30% - 33% [10] [11]. Rivaroxaban has an estimated systemic clearance of about 10 L/h. Its elimination from plasma is characterized by a terminal half-life of 5 to 9 hours in younger individuals, which is prolonged to approximately 11 to 13 hours in elderly patients [4] [13]-[17]. Bleeding is the most commonly reported adverse event in patients receiving rivaroxaban. The most frequently observed types of bleeding include epistaxis (4.5%) and gastrointestinal hemorrhage (3.8%). Severe bleeding events may lead to complications

such as compartment syndrome and renal failure due to hypoperfusion, as well as anticoagulant-related nephropathy [4] [9]-[17].

The purpose of the present study was to assess and compare the pharmacokinetic (PK) profiles and safety of a 20 mg dose of rivaroxaban, using Xarelto® (Batch BXK0F41, expiration date 06/2026; Bayer AG, Germany) as the reference (R) formulation and Asarap® (Batch 012, expiration date 05/2025; Laboratorios Leti S.A.V., República Bolivariana de Venezuela) as the test (T) formulation, in healthy adult volunteers under both fasting and fed conditions.

2. Materials and Methods

2.1. Ethical Considerations

The study was conducted in accordance with ethical standards and regulatory requirements, including the ICMR Guidelines (2017) [18] and the New Drugs and Clinical Trials Rules (2019), India [19]. It also adhered to the ethical principles outlined in the Declaration of Helsinki [20] and the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines [21].

2.2. Subjects

Although the study was open to both men and women, based on previous evidence indicating no significant differences in rivaroxaban pharmacokinetics between sexes [4] [9] [10], only male subjects met all the inclusion criteria.

Eligible participants were healthy males aged 18 to 45 years, with good general health confirmed by a complete clinical history obtained within six months prior to study initiation. Subjects were required to have normal laboratory values based on medical history and physical examination at screening, as well as normal vital signs (blood pressure, pulse rate, and axillary temperature) and physical examination findings. Additional inclusion criteria included prothrombin time (PT) and activated partial thromboplastin time (aPTT) within normal ranges; creatinine clearance (CrCl) greater than 50 mL/min; negative test results for hepatic transaminases, hepatitis B and C, HIV, and VDRL; and a normal 12-lead electrocardiogram (ECG) performed within six months prior to study start. Participants were also required to have normal chest radiographs and negative urine drug screening results.

Subjects with a body mass index (BMI) between 18 and 30 kg/m² were eligible for inclusion, as well as non-smokers or smokers who had abstained from smoking for at least 10 hours prior to the start of the study. All participants were informed about the study procedures, including potential risks, laboratory tests, electrocardiograms, and reimbursement for travel and meals. Written informed consent was obtained from all subjects prior to participation. Exclusion criteria included a history of hypersensitivity to rivaroxaban or any related medications, as well as the presence or history of cardiovascular, renal, hepatic, metabolic, gastrointestinal, neurological, endocrine, hematopoietic, psychiatric, or other organic abnormalities.

Additional exclusion criteria included the use of medications that could interfere with the quantification or pharmacokinetics of the study drug, or the use of potentially toxic medications within 30 days prior to study initiation. Subjects with exposure to known inducers or inhibitors of hepatic enzyme systems were also excluded, as well as those who had taken any medication within 7 days or within five half-lives, whichever was longer prior to the start of the study. Participants were excluded if they had been hospitalized for any reason or had experienced a serious illness within 90 days prior to enrollment, had received any investigational drug within 30 days before the study, or had donated or lost 450 mL or more of blood within 90 days prior to study initiation. Further exclusion criteria included a recent history of drug or alcohol abuse; consumption of caffeine or methylxanthine containing products (e.g., cola beverages containing caffeine, theobromine, or theophylline) within 48 hours prior to dosing; and ingestion of grapefruit juice within 72 hours prior to the study.

2.3. Study Design

This study comprised two independent clinical trials conducted under fasting and fed conditions. Each trial was designed as a randomized, open-label, single-dose, two-treatment, two-sequence, four-period replicate crossover bioequivalence study. Such designs are widely recommended for the evaluation of highly variable drugs, defined by an intra-subject coefficient of variation (ISCV) of $\geq 30\%$. The replicate crossover approach enables direct estimation of within-subject variability for the reference product, thereby supporting the application of scaled bioequivalence methods. In this design, each subject received both the test (T) and reference (R) formulations twice, allowing for a more robust characterization of intra-subject variability and improving the precision of bioequivalence assessment.

Both trials were conducted at the Phase I screening unit, clinical research center, and bioanalytical facility of ICBio Clinical Research Private Limited, India. In each trial, subjects were randomly assigned in a 1:1 ratio to one of two treatment sequences: T-R-T-R or R-T-R-T, where T represents the test formulation and R the reference formulation. The randomization schedule was generated SAS[®] Statistical Software version 9.4 from SAS Institute, Inc., Cary, USA. Subjects assigned to the T-R-T-R sequence received the test product in the first period, followed by the reference formulation in the second period, continuing in an alternating manner across all four periods. Conversely, subjects in the R-T-R-T sequence received the treatments in the reverse order. A washout period of five days was implemented between consecutive treatment periods in both the fasting and fed studies.

Under fasting conditions, each subject received a single oral dose of either the test or reference tablet, administered with 240 mL of water following an overnight fast of at least 10 hours. Subjects remained seated, except for a supine rest period at 2 hours post-dose.

Under fed conditions, subjects received a standardized high-fat meal (≥ 900 kcal per meal with 50% from fat) 30 minutes prior to drug administration and subsequently followed the same dosing and post-dose procedures as in the fasting state. Water intake was restricted for 1 hour before and 1 hour after drug administration; outside this interval, water was permitted without restriction, *ad libitum*. Standardized meals (lunch, snack, dinner, and late meal) were provided at 4, 8, 12, and 24 hours post-dose in each study period.

A total of 22 blood samples (6 mL each) were collected from each subject during each period via an indwelling cannula at pre-dose and at 0.50, 1.00, 1.50, 2.00, 2.33, 2.66, 3.00, 3.33, 3.66, 4.00, 4.33, 4.66, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, and 48.00 hours post-dose. The 24- and 48-hour samples were obtained by direct venipuncture. These procedures were identical under both fasting and fed conditions.

The total duration of the clinical phase was 19 days, from check-in for Period I to the post-study safety assessment. For the fasting study, the first dose was administered on May 03, 2024 to Period I, and the last dose on May 18, 2024 to Period IV (check in May 02, and post assessment date May 20). For the fed study the first dose was administered on May 07, 2024 to Period I, and the last dose was administered on May 22, 2024 (check in May 06, and post assessment date May 24, 2024).

2.4. Analytical Procedure

Blood samples were collected in pre-labelled K₂EDTA vacutainers and centrifuged at 4000 rpm for 10 minutes at 2°C - 8°C. Plasma was separated, appropriately labelled, and stored at $-70^{\circ}\text{C} \pm 5^{\circ}\text{C}$ until analysis. Prior to analysis, plasma samples, calibration standards, internal standard (IS; rivaroxaban-D4, Vivian Life Sciences Private Limited, Mumbai, India), and quality control (QC) samples were thawed and vortex-mixed. For sample preparation, 250 μL aliquots of plasma were combined with 250 μL of extraction buffer and vortexed. Solid-phase extraction was performed using cartridge-based methodology. The cartridges were conditioned with 1 mL of methanol and equilibrated with 1 mL of water before sample loading. Following loading, cartridges were washed with 1 mL of water and 1 mL of washing solution and then dried. Elution was performed using 800 μL of methanol, and the eluate was subsequently diluted with 200 μL of methanol.

Calibration curve standards were prepared by spiking known concentration of rivaroxaban in human plasma. Preparation of rivaroxaban and IS stock solutions were made as Method SOP N° MV.085-00. CC standards were prepared by bulk spiking of CC spiking solutions of analyte using pooled human plasma and stored in deep freezer ICBio II/ULTF/0050 at $-70^{\circ}\text{C} \pm 15^{\circ}\text{C}$. The acceptance criteria was established as deviations from the nominal concentration should be less than or equal to 20% for LLOQ and 15% for all other calibration curve standards (CCS), the coefficient of linear correlation (r) must be ≥ 0.99 , and at least 75% of non-zero CCS should comply with the above criteria including lowest and highest calibra-

tion standards. To inter batch calibration standard precision (%CV) the range was 1.81% to 4.19% and Inter-batch calibration standard accuracy (%nominal) was 94.44% to 106.92%.

Calibration standards were prepared over a concentration range of 1.287 to 1204.829 ng/mL, with QC samples spiked with the internal standard. Processed analyte samples, IS, and QC samples were transferred into pre-labelled vials and placed in the autosampler maintained at $10^{\circ}\text{C} \pm 3^{\circ}\text{C}$. Quantification of rivaroxaban was carried out using an LC-ESI-MS/MS system (Shimadzu LCMS-8040, Mumbai, India). Chromatographic separation was achieved using a BDS Hypersil C18 column (4.6×50 mm, $5 \mu\text{m}$; Thermo Scientific, Mumbai, India). The mass spectrometer was operated in positive electrospray ionization mode. Detection was performed using multiple reaction monitoring (MRM) transitions of m/z 436.10 $\rightarrow$ 145.05 for rivaroxaban and m/z 440.20 $\rightarrow$ 145.00 for the internal standard.

2.5. Statistical and Pharmacokinetics Analyses

The statistical analysis was performed using the SAS[®] Statistical Software version 9.4 from SAS Institute, Inc., Cary, USA. Descriptive statistics were used to summarize plasma concentrations at each sampling time point and pharmacokinetic parameters for each subject. These statistics included the mean, standard deviation, coefficient of variation, geometric mean, median, and range of each product at each adjusted sampling time point. To evaluate the pharmacokinetic parameters, an analysis of variance (ANOVA) was performed on the natural logarithm (ln)-transformed values of C_{max} , AUC 0-t and AUC 0-inf for rivaroxaban. These parameters were analyzed using SAS[®] Statistical Software version 9.4 from SAS Institute, Inc., Cary, USA. ANOVA models were applied for each pharmacokinetic parameter, and the main effects were tested at 0.05 level of significance using mean square, standard deviation, media, minimum and maximum value.

To evaluate bioequivalence, Shuirmann's Two One-Sided t-test, were employed at a 5% level of significance. These tests compared the average pharmacokinetic parameters for T and R formulations, focusing on the ln-transformed values of C_{max} , AUC 0-t and AUC 0-inf for rivaroxaban. The 90% confidence intervals (CI) for differences between treatments were calculated, providing a statistical range within which the true value of the difference lies with high confidence. Geometric Mean Ratio (GMR) for the ln-transformed pharmacokinetic parameters were performed. The difference between the T and R formulations was expressed as "Test-Reference" and the ratio of means (T/R) was obtained by taking the anti-log value of difference of the Geometric Mean Ratios (GMRs) for the PK parameters. Intra subject coefficient of variation (ISCV) for each PK variable and the power was calculated.

Sample size was determined based on the intra-subject coefficient of variation (CV%) for rivaroxaban, as reported in the published literature, including Tao *et al.* [22]-[24]. The intra-subject variability (CV%) for both C_{max} and AUC was approximately 30% - 33%. Assuming a CV% not exceeding 33% for both primary

pharmacokinetic parameters, and that the true T/R ratio would fall within the accepted bioequivalence range (80% - 125%), with an expected ratio of 0.94 - 1.06, a minimum of 34 evaluable subjects was required to demonstrate bioequivalence with a statistical power greater than 90% at a 5% significance level. To account for potential dropouts or withdrawals, additional subjects were enrolled, resulting in a total of 36 subjects under fasting conditions and 40 subjects under fed conditions. Given the particular interest in the fed condition, the sample size for this arm was further increased to ensure an adequate number of evaluable subjects.

2.6. Safety Assessment

The safety of both formulations was evaluated through the assessment of adverse events (AEs). Vital signs, including body temperature, blood pressure, and heart rate, were measured at screening, baseline, and at the end of the study. Twelve-lead electrocardiograms (ECGs) and clinical laboratory tests, including urinalysis, blood biochemistry, and hematology, were performed at screening and at 48 hours post-dose in both bioequivalence studies.

3. Results

3.1. Demographic Data

A total of 35 healthy adult male subjects completed all four periods of the fasting study, while 38 subjects completed the fed study. These subjects were included in the pharmacokinetic (PK) analysis and safety evaluation. The demographic characteristics of the subjects who completed the bioequivalence study under fasting and fed conditions are summarized in **Table 1**.

Table 1. Demographic profile of all subjects that completed the study.

Condition Variable	Fasting condition (n = 35/36)				Fed condition (n = 38/40)			
	Mean	SD	min	max	Mean	SD	min	max
Age (years)	35.36	6.20	19	44	36.48	5.37	25	44
Height (m ²)	1.67	0.06	1.55	1.82	1.68	0.05	1.60	1.69
Weight (Kgs)	69.72	8.69	52	86	71.25	9.63	52	95
BMI (kg/m ²)	25.10	3.07	18.65	29.76	25.32	3.20	18.87	29.98

BMI = Body Mass Index, SD = standard deviation, min = minimum value, max = maximum value. N = evaluable subjects/included.

All subjects were Asian, male, non-smokers, and non-alcohol users.

3.2. Pharmacokinetic Analysis

3.2.1. Fasting Condition Efficacy Analysis

Thirty-five (35) subjects were included in the statistical analysis. The mean pharmacokinetic (PK) parameters of rivaroxaban for the reference formulation (R) and the test formulation (T) are summarized in the tables below. The PK param-

eters presented in **Table 2** were individually derived for each subject from the plasma concentration-time profiles of rivaroxaban. A non-compartmental analysis was applied for the estimation of pharmacokinetic parameters. $C_{\max}$, AUC_{0-t} , AUC_{0-inf} , $T_{\max}$, $T_{1/2}$, λ_z (h^{-1}) and Extrapolated AUC (%) of rivaroxaban in plasma concentration are presented in **Table 2**.

Table 2. Pharmacokinetic parameters after a single rivaroxaban 20 mg oral dose of T and R formulations. Fasting condition. Non-Compartmental model (n = 35).

PK Parameters (Units)	Mean $\pm$ SD Un-transformed data	
	Test (T)	Reference (R)
$C_{\max}$ (ng/mL)	329.89 $\pm$ 105.87	309.91 $\pm$ 118.94
AUC_{0-t} (ng* h/mL)	2700.78 $\pm$ 827.69	2516.17 $\pm$ 1029.64
AUC_{0-inf} (ng* h/mL)	2830.76 $\pm$ 827.82	2643.16 $\pm$ 1017.79
λ_z (h^{-1})	0.09 $\pm$ 0.02	0.09 $\pm$ 827.69
$T_{1/2}$ (h)	8.22 $\pm$ 2.83	8.17 $\pm$ 2.89
$T_{\max}$ (h)	2.55 $\pm$ 0.96	2.70 $\pm$ 1.10
Extrapolated AUC (%)	4.94 $\pm$ 5.28	5.37 $\pm$ 5.39
$T_{\max}$ (h)	2.33 (0.50 - 4.66)	2.66 (0.50 - 4.66)

$C_{\max}$: maximum plasma concentration; AUC_{0-t} : area under the plasma concentration-time curve from time 0 to the last measurable concentration; AUC_{0-inf} : area under the plasma concentration-time curve from time 0 to infinity; $T_{\max}$: time to reach $C_{\max}$; λ_z : terminal elimination rate constant; $t_{1/2}$: time required for the plasma concentration to decrease by 50%. Values are expressed as mean $\pm$ SD, except for $T_{\max}$, which is presented as median (range). Min: minimum; max: maximum; h: hours.

The mean $C_{\max}$, AUC_{0-t} and AUC_{0-inf} values were 329.89 ng/mL, 2700.78 ng*h/mL, and 2830.76 ng*h/mL for the T formulation, compared with 309.91 ng/mL, 2516.17 ng*h/mL, and 2643.16 ng*h/mL for the R formulation. The median $T_{\max}$ was similar between formulations, occurring at 2.55 hours for the T and 2.70 hours for the R formulation.

Figure 1 and **Figure 2**, show the mean plasma concentration-time profile of rivaroxaban 20 mg oral tablets depicted on arithmetic and logarithmic scales, respectively.

For rivaroxaban, the T/R (T/R) ratio, expressed as GMRs of the ln-transformed PK parameters $C_{\max}$, AUC_{0-t} and AUC_{0-inf} were 107.70 (90% CI: 99.85 - 116.17), 109.35 (90% CI: 102.52 - 116.63), and 108.85 (90% CI: 102.48 - 115.61), respectively (**Table 3**). These values fall within the accepted 90% confidence interval range of 80% - 125%, in accordance with FDA guidelines [23]. The intra-subject coefficient of variation (ISCV) for $C_{\max}$, AUC_{0-t} and AUC_{0-inf} was 27.26%, 23.04%, and 21.49%, respectively.

The power of the test for Ln-transformed pharmacokinetic parameters $C_{\max}$ was 99.92% and for AUC_{0-t} and AUC_{0-inf} 100% respectively, **Table 3**.

Based on the above results the T formulation is bioequivalent to the R formulation in healthy adults subjects under fasting conditions.

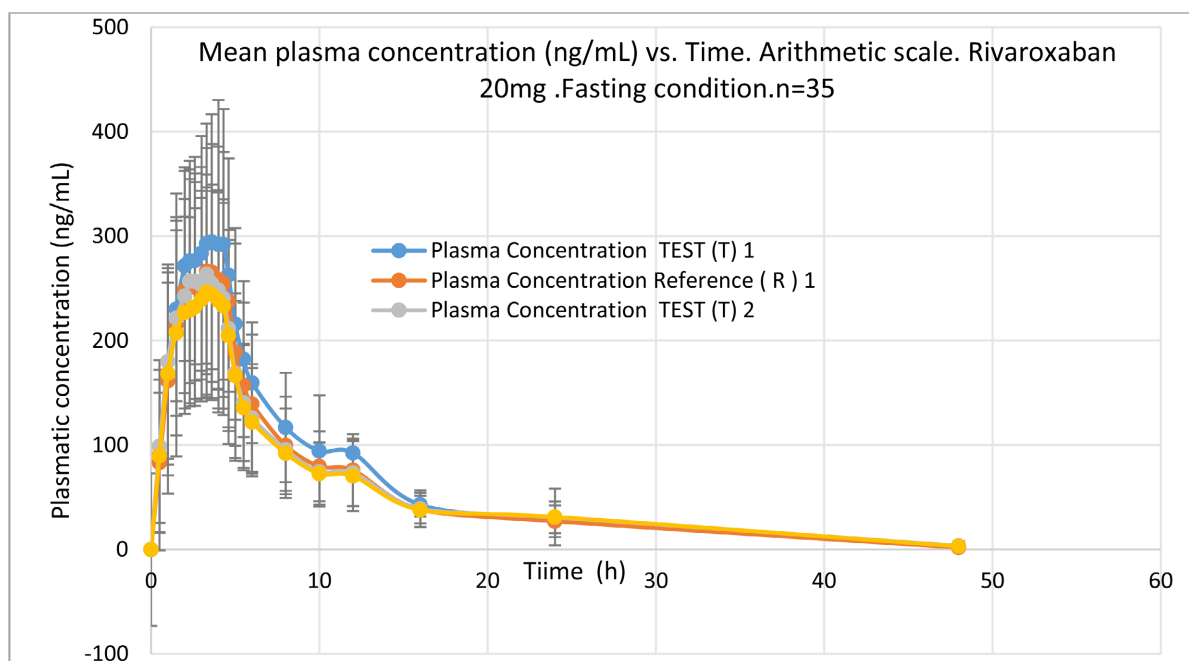


Figure 1. Mean plasma concentration-time profiles of rivaroxaban on an arithmetic scale following a single oral dose in a randomized, crossover study with two treatments, two sequences, and four periods in fasting condition. Test formulations (T1 and T2): Asarap® 20 mg (Laboratorios Leti S.A.V.). Reference formulations (R1 and R2): Xarelto® 20 mg (Bayer AG, Germany).

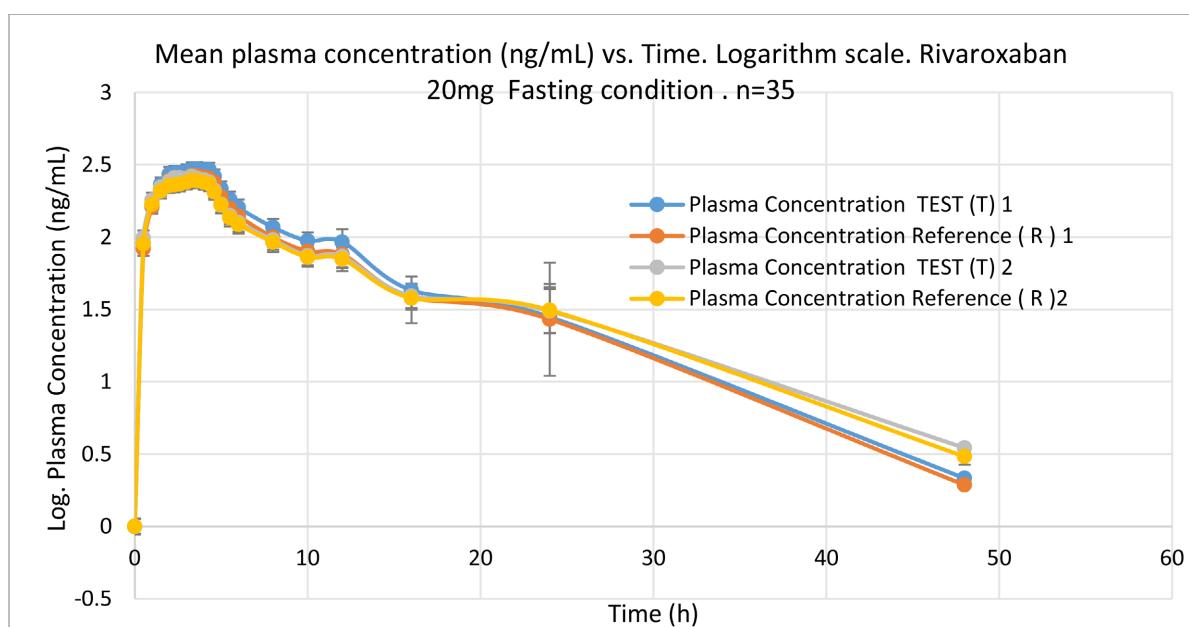


Figure 2. Mean plasma concentration-time profiles of rivaroxaban on a logarithm scale following a single oral dose in a randomized, crossover study with two treatments, two sequences, and four periods in fasting condition. Test formulations (T1 and T2): Asarap® 20 mg (Laboratorios Leti S.A.V.). Reference formulations (R1 and R2): Xarelto® 20 mg (Bayer AG, Germany).

Table 3. Pharmacokinetic Parameters ($C_{\max}$, AUC_{0-t} and AUC_{0-inf}) of rivaroxaban 20 mg, Fasting condition: Geometric Mean Ratio, 90% Confidence Intervals, ISCV (%) and Power (%) ($n = 35$).

PK Parameters (Units)	Ln-transformed Geometric Mean Ratio (GMR)			90% Confidence Interval (CI) (Min-Max)	ISCV (%)	Power (%)
	Test (T)	Reference (R)	T/R (%)			
$C_{\max}$ (ng/mL)	312.86	290.48	107.70	(99.85 - 116.17)	27.26	99.92
AUC_{0-t} (ng*h/mL)	2577.05	2356.74	109.35	(102.52 - 116.63)	23.04	100.00
AUC_{0-inf} (ng*h/mL)	2716.57	2495.75	108.85	(102.48 - 115.61)	21.49	100.00

$C_{\max}$: maximum plasma concentration, AUC_{0-t} : area under the plasma concentration–time curve from time 0 to the last measurable concentration; AUC_{0-inf} : area under the plasma concentration–time curve from time 0 to infinity, CI: confidence intervals, ISCV Intra-subject coefficient of variation Ln: natural logarithm.

3.2.2. Fed Condition Analysis of Efficacy

A total of 40 subjects were enrolled in the fed study, of whom 38 completed all four periods of the clinical phase. The pharmacokinetic variables are summarized in **Table 4**.

Table 4. Pharmacokinetic of mean formulation for rivaroxaban 20 mg. Fed condition Non-Compartmental model ($n = 38$).

Pharmacokinetic Parameters (Units)	Mean $\pm$ SD (Un-transformed data)	
	Test (T)	Reference (R)
$C_{\max}$ (ng/mL)	465.98 $\pm$ 126.74	453.60 $\pm$ 108.02
AUC_{0-t} (ng*h/mL)	3405.30 $\pm$ 1016.90	3414.93 $\pm$ 841.89
$AUC_{0-\infty}$ (ng*h/mL)	3501.70 $\pm$ 1002.75	3509.13 $\pm$ 838.52
λ_z (h^{-1})	0.133 $\pm$ 0.034	0.129 $\pm$ 0.031
$t_{1/2}$ (h)	5.59 $\pm$ 1.66	5.76 $\pm$ 1.84
$T_{\max}$ (h)	3.91 $\pm$ 0.75	3.81 $\pm$ 1.051
Extrapolated AUC (%)	2.96 $\pm$ 2.27	2.80 $\pm$ 1.95
Median (Min, Max)		
$T_{\max}$ (h)	4.00 (1.50 - 5.00)	4.33 (0.50 - 5.50)

$C_{\max}$, maximum plasma concentration, AUC_{0-t} , area under the plasma concentration–time curve from time 0 to the last measurable concentration; AUC_{0-inf} , area under the plasma concentration–time curve from time 0 to infinity, $T_{\max}$ time to reach $C_{\max}$, λ_z fraction eliminated per unit of time, $T_{1/2}$ time required for plasma concentration to decrease by 50%. *Median (range) min: minimum, max: maximum, h: hours.

Figure 3 and **Figure 4** illustrate the mean plasma concentration–time profiles of rivaroxaban 20 mg oral tablets for both the T and R formulations under fed conditions, displayed on arithmetic and logarithmic scales, respectively.

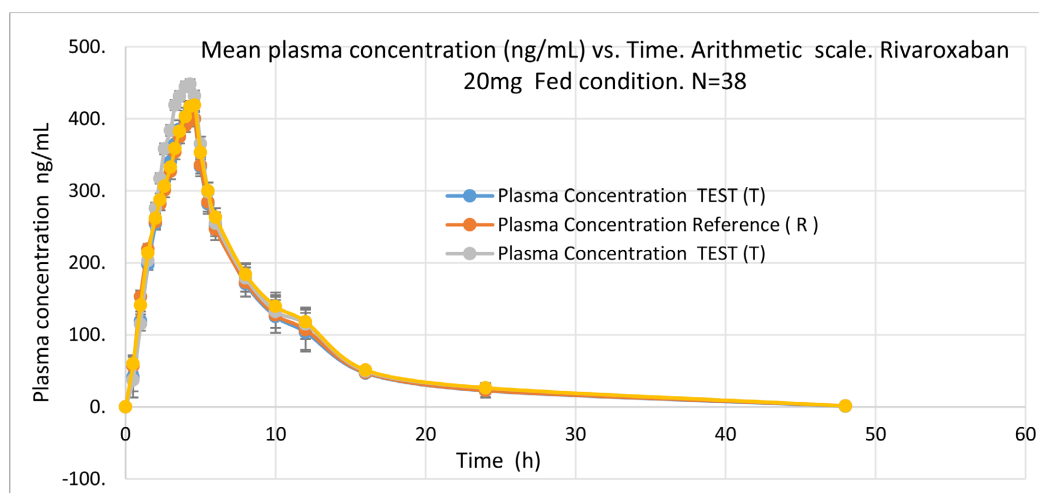


Figure 3. Mean plasma concentration-time profiles of rivaroxaban on an arithmetic scale following a single oral dose in a randomized, crossover study with two treatments, two sequences, and four periods in fed condition. Test formulations (T1 and T2): Asarap® 20 mg (Laboratorios Leti S.A.V.). Reference formulations (R1 and R2): Xarelto® 20 mg (Bayer AG, Germany).

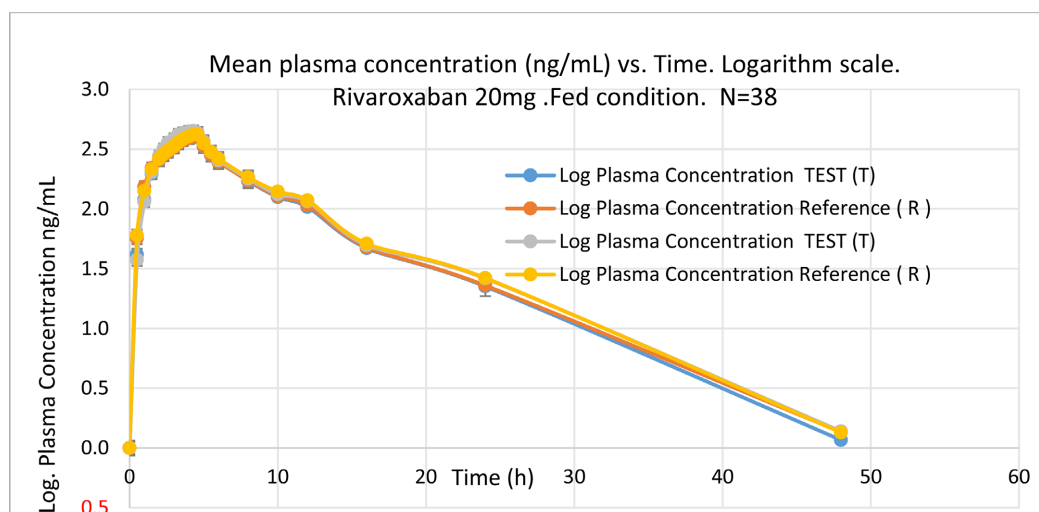


Figure 4. Mean plasma concentration-time profiles of rivaroxaban on a logarithm scale following a single oral dose in a randomized, crossover study with two treatments, two sequences, and four periods in fed condition. Test formulations (T1 and T2): Asarap® 20 mg (Laboratorios Leti S.A.V.). Reference formulations (R1 and R2): Xarelto® 20 mg (Bayer AG, Germany).

Table 5. Pharmacokinetic Parameters (C_{max} , AUC_{0-t} and $AUC_{0-\infty}$) of rivaroxaban 20 mg. Fed condition Geometric Mean Ratio, 90% Confidence Intervals, ISCV (%) and Power (%) (N = 38).

Pharmacokinetic Parameters (Units)	Ln-transformed Geometric Mean Ratio (GMR)			90% Confidence Interval (Parametric) CIs Rank	ISCV (%)	Power (%)
	Test Media (T)	Reference Media (R)	T/R (%)			
C_{max} (ng/mL)	451.35	441.68	102.19	(97.87 - 106.70)	15.95	100.00
AUC_{0-t} (ng*hr/mL)	3277.83	3321.38	98.69	(95.37 - 102.13)	12.79	100.00
$AUC_{0-\infty}$ (ng*hr/mL)	3380.47	3418.96	98.87	(95.67 - 102.18)	12.29	100.00

C_{max} : maximum plasma concentration, AUC_{0-t} : area under the plasma concentration-time curve from time 0 to the last measurable concentration; $AUC_{0-\infty}$: area under the plasma concentration-time curve from time 0 to infinity, CI: confidence intervals, ISCV Intra subject coefficient of variability. Ln: natural logarithm.

All PK parameters (C_{max} , AUC_{0-t} and AUC_{0-inf}) exhibited GMRs (T/R) and corresponding 90% confidence intervals within the predefined regulatory acceptance range of 80% - 125% [23], thereby demonstrating bioequivalence between the Test (T) and Reference (R) formulations under fed conditions. The within-subject variation (ISCV) for log-transformed PK parameters was estimated using an analysis of variance (ANOVA) model. Under fed conditions, the ISCV was 15.75% for C_{max} , 12.79% for AUC_{0-t} and 12.29% for AUC_{0-inf} parameters. These findings indicate low intra-subject variation, as reflected by the ISCV values, in comparison with the higher variation typically reported under fasting condition study, **Table 3** and **Table 5** and as described in the literature [4] [10]-[13] [16] [17] [22].

3.3. Safety Results Fasting and Fed Conditions

3.3.1. Safety Results

Subjects were monitored for adverse events throughout the study (fasting and fed). Vital signs (blood pressure, pulse rate, respiratory rate and ancillary/body temperature) were checked and evaluated before, during and at the end of study. The investigator did clinical examination of the subjects at the time of screening and during the check-out in each period. At the end of these studies, a safety evaluation was done which included hematology and clinical bio-chemistry laboratory. No adverse events or serious adverse events were reported.

3.3.2. Withdrawal and Drop Outs

In the fasting study, subject No. 09 (S09, sequence T-R-T-R) did not report to the clinical site for period II check-in due to a family issue and was therefore considered a dropout. For the fed study, subject S19 (sequence T-R-T-R) did not report to the clinical site for period II, and subject S23 (sequence T-R-T-R) did not report for period III. Both absences were due to personal reasons, and both subjects were considered dropouts from the study.

4. Discussion

Rivaroxaban is the first direct oral anticoagulant (DOAC) approved as a first-line therapy in patients with atrial fibrillation (AF), except in those with moderate-to-severe mitral stenosis or mechanical heart valves [3] [4] [6]. Clinical trials comparing DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) with warfarin have demonstrated either superiority or non-inferiority in the prevention of stroke or systemic embolism among patients with AF [3] [5]-[8].

Regulatory agencies such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) approved rivaroxaban for pediatric use between 2020 and 2021 for the treatment of venous thromboembolism (VTE) and the prevention of recurrent VTE in children and adolescents under 18 years of age [3] [7] [8]. Additionally, the FDA has approved rivaroxaban for thromboprophylaxis in children aged 2 years and older with congenital heart disease who have undergone the Fontan procedure [7] [8].

This bioequivalence (BE) study was conducted in accordance with U.S. FDA

guidelines specific to rivaroxaban, using a 4-period, 2-sequence, fully replicated crossover design under both fasting and fed conditions to assess the within-subject variability of the test and reference formulations [23]. In these studies, the 20 mg oral rivaroxaban T and R formulations demonstrated higher intra-subject coefficient of variation (ISCV) under fasting conditions (27.6% for C_{max} , 23.04% for AUC_{0-t} , and 21.49% for AUC_{0-inf}). Under fed conditions, the ISCV values were 15.95% for C_{max} , 12.79% for AUC_{0-t} , and 12.29% for AUC_{0-inf} . These findings are consistent with values reported in other bioequivalence studies [4] [9]-[13]. The higher intra-subject variability observed for rivaroxaban under fasting conditions is mainly related to its low solubility (BCS class II), making absorption dependent on gastrointestinal dissolution. In the absence of food, reduced bile secretion, variable fluid volume, and less stable gastrointestinal conditions lead to inconsistent drug dissolution and absorption. Conversely, food intake enhances bile secretion, prolongs gastrointestinal residence time, and stabilizes luminal conditions, resulting in improved solubilization, more consistent absorption, and reduced PK variability.

Statistical analysis of evaluable data from 35 subjects under fasting conditions and 38 subjects under fed conditions demonstrated that the 90% confidence intervals (CIs) for the pharmacokinetic parameters were entirely within the predefined bioequivalence acceptance range of 80% - 125%.

Given the continued and expanding use of rivaroxaban, it is essential to ensure the availability of high-quality generic formulations supported by bioequivalence studies, particularly in Latin American countries, where improving access to effective medicines remains a public health priority [25]-[30].

5. Limitations

We were unable to assess pharmacokinetic parameters in female volunteers. Although the study protocol allowed the inclusion of both male and female subjects, only male participants were enrolled, as they were the only individuals who responded to the screening call. It is important to note that previous studies with rivaroxaban have not demonstrated clinically significant differences in pharmacokinetic parameters between male and female subjects. Therefore, the absence of female participants is not expected to have a meaningful impact on the overall interpretation of the pharmacokinetic and bioequivalence results.

6. Conclusions

The results of these studies confirm the bioequivalence of the two tested rivaroxaban 20 mg formulations, Asarap® (Laboratorios Leti S.A.V.) as the Test formulation and Xarelto® (Bayer A.G.) as the Reference formulation. The 90% confidence intervals for the GMR T/R of C_{max} , AUC_{0-t} , and AUC_{0-inf} were within the predefined bioequivalence acceptance range of 80% - 125%.

Both rivaroxaban 20 mg oral tablets, T and R formulations were bioequivalent and well tolerated in healthy volunteers under both fasting and fed conditions.

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Author Contribution

E.P., A.O., and J.CH performed the statistical analysis and interpretation, and wrote, revised, and approved the manuscript.

Declaration of Patient Consent

All volunteers provided written informed consent after being well informed about the study before screening.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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