Journal of Biosciences and Medicines, 2024, 12, 230-243
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Pharmacokinetics and Bioequivalence Evaluation of Two Rosuvastatin Calcium 20 mg Tablets: A Single Oral Dose, Randomized-Sequence, Open-Label, Two-Period Crossover Study in Healthy Volunteers under Fasting Conditions

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How to cite this paper: Pena, E., Inatti, A. and Chacón, J.G. (2024) Pharmacokinetics and Bioequivalence Evaluation of Two Rosuvastatin Calcium 20 mg Tablets: A Single Oral Dose, Randomized-Sequence, Open-Label, Two-Period Crossover Study in Healthy Volunteers under Fasting Conditions. *Journal of Biosciences and Medicines*, **12**, 230-243.
https://doi.org/10.4236/jbm.2024.126020

Received: April 30, 2024
Accepted: June 22, 2024
Published: June 25, 2024

Abstract

Objectives: To compare the rate and extent of absorption of Racor® 20 mg (Rosuvastatin calcium 20 mg) tablet of Laboratorios Leti, S.A.V., with Crestor® 20 mg (Rosuvastatin calcium 20 mg) tablet of AstraZeneca, UK Limited in healthy adult human subjects under fasting conditions. **Method:** This was an open label, analyst blind, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study in healthy, adult, human subjects under fasting condition. Twenty-four (24) subjects were planned as per the protocol and all subjects completed both periods of the study. The concentrations of Rosuvastatin in plasma were quantitated using a validated LC-MS/MS method of analysis and plasma levels were submitted for statistical analysis. C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, T_{max}, $t_{1/2}$, K_{el} (hrs^{-1}), percent AUC extrapolated [100 * ($AUC_{0\text{-}\infty}$ – $AUC_{0\text{-}t}$)/$AUC_{0\text{-}\infty}$] (AUC_%Extrapobs) were calculated for rosuvastatin in plasma using SAS® version 9.1.3, SAS Institute. Inc. USA.CARY. ANOVA, 90% confidence interval using Schuirmann's two one-sided test for bioequivalence, power and ratio analysis, for ln-transformed pharmacokinetic parameters C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were computed and reported for Rosuvastatin in plasma for BE. **Results:** Data showed that 90% confidence intervals for the test/reference geometric mean ratios (GMR) of C_{max} (95.01 - 112.66), $AUC_{0\text{-}t}$ (93.38 - 111.67) and $AUC_{0\text{-}\infty}$ (93.65 - 111.29) were within the BE (80% - 125%) acceptance range. **Conclusions:** Two products formulation, reference (R) Crestor® (rosuvastatin calcium) of AstraZeneca and

test (T), Racor® (rosuvastatin calcium) of Laboratorios Leti S.A.V., with a single dose of 20 mg, under fasting conditions were bioequivalent. No severe, serious or unexpected adverse events (AEs) were reported in this study.

Keywords

Bioequivalence, Rosuvastatin, Pharmacokinetics.

1. Introduction

Cardiovascular disease (CVD) is the most common cause of death globally, especially in industrialised countries and remains the leading cause of morbidity and mortality worldwide, of which ASCVD is the major component, is responsible for >4 million deaths in Europe each year [1]. It kills more women (2.2 million) than men (1.8 million), although CV deaths before the age of 65 years are more common in men (490,000 vs.193,000). The 2010 Global Burden of Disease study estimated that CVD caused 15.6 million deaths worldwide, 29.6% of all deaths. This was two times as many deaths as was caused by cancer and was more than all communicable, maternal, neonatal, and nutritional disorders combined [1] [2].

Many epidemiological studies have established the relationship between elevated serum levels of total cholesterol and specifically low-density lipoprotein (LDL)-cholesterol in the development of Coronary Heart Disease (CHD) [3] [4]. Dyslipidaemia is also one of the many modifiable major risk factors for stroke and peripheral vascular disease [4] [5]. The US National Cholesterol Education Program Adult Treatment Panel III guidelines emphasise the importance of lowering serum LDL-cholesterol levels as the primary target in cholesterol-lowering therapy [6]. However, in a 1997 US primary care providers survey only 38% of all patients met the NCEP-defined target serum LDL-cholesterol goal [7].

Rosuvastatin is a synthetic HMG-CoA reductase inhibitor with unique pharmacologic and pharmacokinetic properties [8]-[11]. Its chemical structure is 3R,5S,6E)-7-[4-(4-Fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)-amino]-5-pyrimidinyl]-3,5-dihydroxy-6-heptenoic acid calcium salt. The empirical formula is (C22H27FN3O6S)2Ca and the molecular weight is 1001.14 g/mol. It has additional HMG-CoA reductase enzyme-binding interactions that cause tighter binding, has substantial active transport into hepatocytes, and has the lowest IC_{50} for sterol synthesis in hepatocytes [9] [12]. The affinity of rosuvastatin for the active site of the enzyme is four times greater than the affinity of HMGCoA for the enzyme [13]. It is used in conjunction with a healthy diet and regular sport activities to treat patients with primary hyperlipidemia and mixed dyslipidemia to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C, additionally in patients with hypertriglyceridemia, primary dysbetalipoproteinemia (Type III hyperlipoproteinemia), patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, total-C, and ApoB, to slow the

progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C as an adjunct to diet, pediatric patients 10 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH) to reduce elevated total-C, LDL-C and ApoB after failing an adequate trial of diet therapy and to risk reduction of MI, stroke, and arterial revascularization procedures in patients without clinically evident CHD, but with multiple risk factors [12]. Rosuvastatin is hydrophilic relative to most other statins (excluding pravastatin) with a logD at pH 7.4 of −0.33 [14].

In a group of randomised, placebo-controlled, double-blind trials in healthy male volunteers who received single doses of rosuvastatin 20 to 80 mg (XII International Symposium on Atherosclerosis, Stockholm, Sweden, June 2000), rosuvastatin exhibited a roughly linear relationship between dose and both maximum plasma drug concentration (C_{max}) and mean steady-state area under the concentration-time curve, from 0 to 24 hours after administration ($AUC_{0\text{-}24}$) [15]. There was no relevant steady-state accumulation. At steady state, after 7 days treatment with rosuvastatin 40 mg daily, the C_{max} was 37.0 μg/L and time to reach Cmax was 3 hours [15]. The mean elimination half-life was 20.8 hours with an $AUC_{0\text{-}24}$ of 256 μg/L·h [15]. The peak plasma concentration (Cmax) of 6.1 ng/ml occurs at 5 hours (t_{max}) after a single oral 20 mg dose [16]. Prolonged dosing with 20 mg of rosuvastatin leads to a steady state C_{max} of 9.7 ng/ml, which occurs 3 hours after dosing [15]. In a compilation of pharmacokinetic trials, the C_{max} and the area under the concentration time curve ($AUC_{0\text{-}24}$) exhibit an approximately linear relation throughout the dosage range of 5 to 80 mg after single and seven daily doses with steady-state t_{max}, ranging from 3 to 5 hours [15]. This t_{max} is qualitatively longer than other currently available statins, which have t_{max} values of ≤ 3 hours [17]. Rosuvastatin is not extensively metabolised in humans [16]. A dominant N-desmethyl product has been identified *in vitro* [18]. The pharmacokinetics of rosuvastatin are not affected by mild to moderate hepatic impairment and appear to have a low propensity for pharmacokinetic drug interactions [19] [20]. The oral bioavailability of rosuvastatin is approximately 20%, or rather lower than cerivastatin (which has a bioavailability of 60%), but higher than lovastatin and simvastatin, and comparable to that of pravastatin, fluvastatin, and atorvastatin. Food is known to reduce rosuvastatin's rate of absorption by 20%, but the extent of absorption is unchanged. This does not reduce the cholesterol lowering potency; therefore, rosuvastatin can be taken with or without food, and in the morning or evening [8] [18].

This study was designed to evaluate the bioequivalence of Racor® 20 mg (Rosuvastatin calcium 20 mg) tablet of Laboratorios Leti, S.A.V., with Crestor® 20 mg (Rosuvastatin calcium 20 mg) tablet of AstraZeneca, UK Limited

2. Methods

2.1. Ethical Considerations

This study was conducted ethically in accordance with the principles of the

Declaration of Helsinki (Brazil, 2.013) and ICH-GCP guidelines [21] [22]. The study protocol and the corresponding informed consent form (ICF) used to obtain consent from study subjects were reviewed and approved by the "ACE Independent Ethics Committee" as IEC meeting held on 23 May 2023 and submitted on 18 May 2023. All subjects participating received full details of the study in verbal and written in English and/or native (Kannada) language by the medically qualified study personnel who is trained in study protocol.

Written approval for the protocol with the corresponding ICF was obtained from the Independent Ethics Committee before the first administration of study medication.

2.2. Study Design

The study was an open label, analyst blind, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, BE study performed in healthy adult subjects under fasting conditions. Tablets of Crestor® (rosuvastatin calcium) Batch 78,789, expiration date 03/2024, AstraZeneca, S.A. de C.V. Lomas Verdes, Mexico, were used as the reference (R) sample and Racor® (rosuvastatin calcium) batch RE-0369-01, expiration date 01/2025, rosuvastatin calcium 20 mg, as the active pharmaceutical ingredient (API). Following an overnight fast of at least 10 hrs, subjects received a single dose of T or R formulation after performing a randomization schedule using SAS® 9.1.3 statistical software that ensured balanced allocation to each study period. The clinical phase had a duration of 10 days, (22/06/2023 period I and 02/07/2023 to period II), the subjects who were administered the T product in period I were administered R product in period II and vice versa. There was a washout period of 10 days between the two dosing periods, considering the terminal half-life for rosuvastatin [15]. Male subjects who fulfilled all the following criteria were included in the study, although the study was open to males and females, only male subjects fulfilled all the following inclusion criteria: able to comprehend the nature and purpose of the study and willing to give written informed consent for participation in the study, willing to be available for the entire study period and to comply with protocol requirements, aged between 18 and 45 years, body mass index (BMI) within a range of 18 to 30 kg/m^2 with good health based on the results of a complete clinical history and valid for 1 month prior to the start of the study, normal laboratory values as determined by medical history and physical examination at the time of screening, normal vital signs and physical examination and laboratory, normal chest radiography and negative result in urine drug tests, normal or clinically non-significant 12-lead ECG, negative test for Human Immunodeficiency Virus (HIV) type I/II antibodies, Hepatitis B surface antigen (HBsAg) and Hepatitis C virus (HCV) antibodies, non-smokers and should not have been consuming any kind of tobacco products including chewing or inhaling tobacco in the form of jarda, pan, gutkhaetc, able to read and understand the Informed Consent Document as a whole and communicate effectively if required and were eligible to participate. The main exclusion criteria included: any medical or surgical condition, which might significantly interfere with

the functioning of the gastrointestinal tract or blood-forming organs, history or presence of gastric or duodenal ulcer or GI bleeding or blood in stools anytime in the past, history of severe infection or major surgery in the past 6 months, history of minor surgery or fracture within the past 3 months, significant history or current evidence of malignancy or chronic infectious, cardiovascular, renal, hepatic, ophthalmic, pulmonary, neurological, metabolic (endocrine), hematological, gastrointestinal, immunological or psychiatric diseases, or organ dysfunction, history of hypersensitivity to active principle or any excipient or rosuvastatin, positive urine test for drugs of abuse, any major illness or hospitalization within 90 days prior to check-in of first period, any other clinical condition like diarrhea or vomiting within three days prior to check-in of any period, consumption of xanthine or its derivative containing food or beverages, unusual diet with low sodium intake or abnormal diet, use of any depot injection or an implant of any drug within three months prior to check-in of the first period and throughout the duration of the study until the post study safety sample is collected, participated in any clinical study within the past 90 days prior to check-in, consumption of grapefruit or its juice within 72 hours prior to check-in each study period and throughout sampling time points and use tobacco, alcohol or any medication within the 24 hours (h) prior to study start. All subjects participating in this study received full details of the study before signing the consent forms.

2.3. Drug Administration and Blood Collection

All the subjects were fasted for at least 10 hours (overnight) before they were scheduled for the dosing. Drinking water was not allowed from one hour before dosing till one hour post dosing. A single oral dose (1 × 20 mg tablets) of either the Investigational Product (T) or Reference Product (R) was administered with 240 mL of water at ambient temperature in each period in sequential order from 08:00 to 08:22 hours on 22 Jun 2023 and 02 Jul 2023 for period I and II, respectively, and were in sitting posture for 2 hours after dosing. Thereafter the subjects can resume normal activity but should avoid excessive exertion. During housing the standard meal menu was the same in both periods (2200 Kcal) and was provided at 04.00, 08.00, 12.00 and 24.000 hours after dosing and drinking water was provided *ad libitum.*

A total 20 blood samples of 5 ml were collected from each subjects at each sampling time point, except pre-dose (for pre-dose 7 ml) during period I and II, respectively. The venous blood samples were withdrawn at pre-dose (00.000 hour) and at 01.000, 01.500, 02.000, 02.500, 03.000, 03.500, 03.750, 04.000, 04.250, 04.500, 05.000, 06.000, 08.000, 10.000, 12.000, 14.000, 24.000, 48.000 and 72.000 hours post-dose following drug administration in each period. Equal allocation of treatments or balanced randomization was ensured. The cannula was removed from the subjects in each period at 14.000 hour and 24.000, 48.000 and 72.000 hours samples were collected by direct prick through the vein. 6 ml of blood was collected for post-study safety analysis from each of the subjects after completion of the second period. Post

study sample was carried out at the end of the study to confirm that the study subject was healthy. Before every blood sample collection 0.5 ml of normal saline Blood was discarded through I.V. cannula. After every blood sample collection 0.5 ml of saline was injected into the I.V. cannula to prevent cannula from clogging. The pre-dose blood sample was collected within 1 hour prior to dosing and the post-dose in house samples were collected within ±2 minutes from the scheduled sampling time. The mid-point time of collection of each blood sample (to the nearest minute) was recorded on the appropriate CRF.

2.4. Analytical Procedure

The clinical phase of the study was performed at ICBio Clinical Research Private Limited, #16&18 ICBio Tower, Yelahanka Main Road, Chikkabetahalli, Vidyaranyapura, Bangalore-560097, India.

A Sensitive and Selective LCMS/MS method to quantify Rosuvastatin in K2EDTA human plasma over the concentration range of 2.002 to 80.790 ng/mL respectively was developed and validated using Rosuvastatin D6 as an internal standard. Rosuvastatin was selectively isolated from 400 µl plasma by Solid Phase Extraction followed by evaporation. Estimation was done by mass spectrometric method and chromatographic using BDS Hypersil C18, 4.6 × 100 mm, 5 µm. The objective was to develop and validate a specific LCMS/MS method to determine Rosuvastatin in K2EDTA human plasma using Rosuvastatin D6 as internal standard. Plasma Selectivity was evaluated by analyzing eight independent lots of Biological matrix containing K2EDTA anticoagulant.

The blood samples were collected from study subjects for period I and period II analyte at the clinical facility using vacutainers containing anticoagulant K2EDTA, were centrifuged at 4000 rpm for 10 min at 2˚C - 8˚C, labelled and frozen at −70˚C ± 15˚C as per protocol to stored prior to analysis. A total of 1914 samples in polypropylene tubes were analyzed for detection of Analyte in K2EDTA human plasma with internal standard. Calibration curve (CC) standards were prepared by spiking known concentration of Rosuvastatinin human plasma. CC standards were prepared by bulk spiking of CC spiking solutions of Analyte using pooled human plasma and stored in deep freezer ICBio-II/BA/ULTF/0015 at −70˚C ± 15˚C.

The samples of subjects and Re-assay run were analyzed using a calibration curve range 0.202 to 80.790 ng/mL for rosuvastatin which was the validated range. Quality control samples at low, middle and high levels were prepared by spiking known concentrations of analyte in human plasma. QC samples were prepared by bulk spiking each of QC spiking solutions (HQC, MQC and LQC) of analyte using pooled human plasma and M1QC was pooled and stored in freezer ICBio-II/BA/ULTF/0015 at −70˚C ± 15˚C with appropriate acceptance criteria.

A set of calibration curve standards and quality control samples were removed from the freezer/ultra-low temperature freezer (ULTF/FRZ) and allowed to thaw at room temperature. 50 µl of ISTD dilution was added to all samples except STD

Blank. Aliquots of 0.400 mL of plasma samples and vortexed were added to mix. The samples were mixed with 400 µl of water. Solid phase extraction was performed using the Hi-Purit HLB cartridge. Cartridge conditioning was carried out with 1 ml of methanol and equilibrated with 1 ml of water. The analyte was extracted with 0.700 ml of methanol. The sample was dried in the evaporator at 40˚C ± 2˚C and reconstituted with 0.400 ml of reconstitution solution. An appropriate volume of samples was transferred into pre-labeled autosampler vials, arranged in an autosampler at 10˚C ± 3˚C, and injected using LC-ESIMS/MS.

2.5. Statistical and Pharmacokinetics Analyses

C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were the PK parameters determined for Rosuvastatin and its ln-transformed values were statistically analyzed using SAS® Statistical Software Version 9.1.3 or higher, SAS Institute.Inc., CARY, USA. A general linear model (Proc GLM of SAS®) with the main effects of period and treatment as fixed effects and subject nested within sequence as random effect was used to analyze the Rosuvastatin log-transformed PK parameters.

A separate ANOVA model was used to analyze each of the parameters. Main effects were tested at the 0.05 level of significance against the residual error (mean square error/MSE) from the ANOVA model as the error term. The sample size calculation for this study is based on the observed intra-subject coefficient of variation (CV%) for Racor® 20 mg (Rosuvastatin calcium 20 mg) tablet as obtained from published literature [23]. Based on the referred literature and using the reported 90% confidence intervals, intra-subject CV% was estimated (or back calculated) for the pharmacokinetic parameters of Rosuvastatina 20 mg (Rosuvastatin calcium 20 mg) tablet the maximum intra-subject CV% was observed for Cmax as ~24%. Thus, with the expected coefficients of variation for Cmax and AUC not exceeding 26% and assuming the true ratio falling within 99% to 101% (i.e. a true treatment difference of 1%), the study should have at least 21 evaluable subjects to show the bioequivalence with a power of greater than 80% at 5% level of significance. Three additional subjects were included in the study for possible dropouts/withdrawals.

The geometric mean ratio (GMR) these primary PK parameters (T/R) and the 90% confidence intervals (CIs) were calculated for the determination of BE. Analysis of variance was applied to the logarithm-transformed PK values. BE between the test and reference formulations of Rosuvastatin was demonstrated if the 90% CI fell within the acceptance range of 80% - 125% for ln-transformed pharmacokinetic parameters C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ [24].

2.6. Safety Assessments

Safety of the subjects was evaluated through the assessment of AEs, vital signs and laboratory test (biochemistry, hematology and urianalysis) throughout the study. Vital signs were measured at baseline screening and at the end of the study. Clinical laboratory was carried out at screening and for those subjects who came for period II of the study.

3. Results

3.1. Baseline Characteristics

A total of 24 healthy adult male subjects who met the criteria were enrolled and randomized in the study. All completed the study and were valid for the PK analysis and safety evaluation. Demographic data of all evaluable subjects are presented in Table 1.

Table 1. Demographic data of subjects completing the bioequivalence study.

Baseline Characteristics	Total (N = 24)
Sex (Men)	100%
Age (Year)	36.83 ± 5.12
Weight (kg)	66.04 ± 8.76
Height (m)	1.67 ± 0.07
Body Mass Index (kg/m^2)	23.60 ± 2.52

Results are displayed as n (%) or mean ± standard deviation (SD).

3.2. PK Evaluation

A non-compartmental analysis was applied for the estimation of PK parameters of Rosuvastatin in plasma concentration time data using SAS® software version 9.1.3 (SAS Institute Inc., CARY, USA) (Table 2).

Table 2. Pharmacokinetics parameters after a single Rosuvastatin 20 mg oral dose of T and R formulations.

ANALITE: Rosuvastatine (N = 24)		
PK Parameters	Test (T)	Reference (R)
C_{max} (ng/mL)	25.4603 ± 18.93964	23.1336 ± 10.28288
$AUC_{0\text{-}t}$	206.0026 ± 93.91697	201.1688 ± 79.42444
$AUC_{0\text{-}\infty}$ (ng·h/mL)	213.9627 ± 96.83693	208.3273 ± 79.41463
T_{max} (h)	4.500 (1.000 - 4.500)	4.250 (1.000 - 4.500)
K_{el} (h^{-1})	0.06380 ± 0.030293	0.07012 ± 0.037991
$T_{1/2}$ (h)	12.2041 ± 3.32236	11.7044 ± 3.94483

Data presented as mean ± SE. C_{max}: maximum concentration; $AUC_{0\text{-}t}$: area under the plasma concentration-time curve from time 0 to the last measurable concentration; $AUC_{0\text{-}\infty}$: area under the plasma concentration-time curve from time 0 to infinity; T_{max}: time to reach C_{max}; Kel: elimination rate constant; $T_{1/2}$ time required for plasma.

Mean C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$, were respectively 25.4603 ng/mL, 206.0026 ng·h/mL, 213.9627 ng/mL for the T formultion and 23.1336 ng/mL, 201.1688 ng·h/mL, 208.3273 ng·h/mL for the R formulation. Median T_{max} was 4.500 h for the T and 4.250 h for the R formulations. Mean Rosuvastatine plasma concentration versus time curve for each formulation of Rosuvastatine for T and R formulations are presented in Figure 1 and Figure 2.

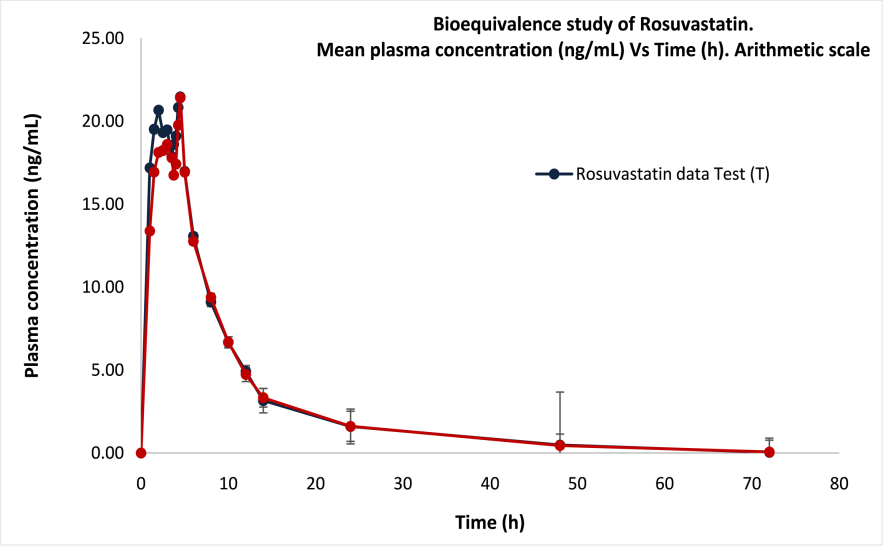

Figure 1. Mean Rosuvastatin 20 mg plasma concentration versus time (h) profile for each formulation is presented in an arithmetic scale, following a single oral dose. Blue line indicates Rosuvastatin (Test product of Laboratorios Leti S.A.V. República Bolivariana de Venezuela), and red line indicates Rosuvastatin (Reference product of AstraZeneca).

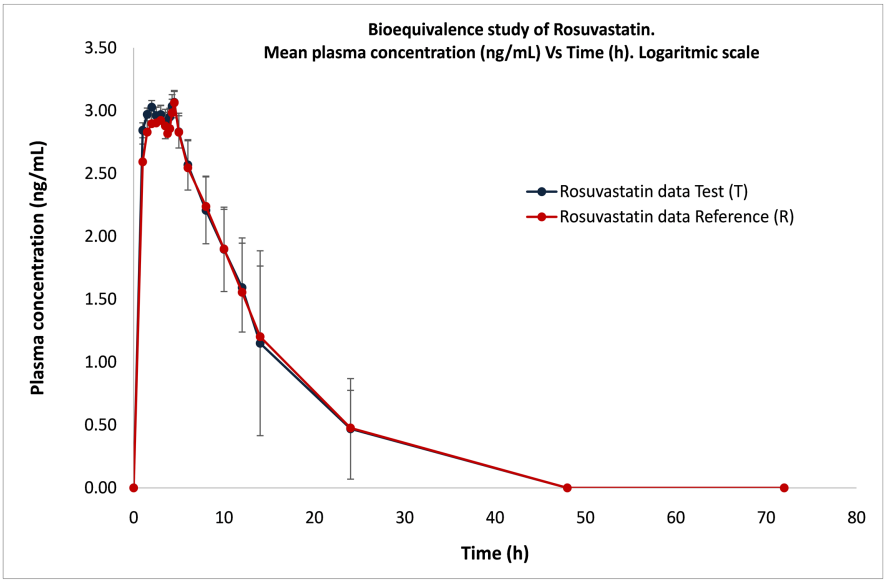

Figure 2. Mean Rosuvastatin 20 mg plasma concentration versus time (h) profile for each formulation are presented in a logarithmic scale, following a single oral dose. Blue line indicates Rosuvastatin (Test product of Laboratorios Leti S.A.V. República Bolivariana de Venezuela), and red line indicates Rosuvastatin (Reference product of AstraZeneca).

3.3. Bioequivalence

Analysis of variance for ln-transformed in PK parameters: C_{max} (ng/mL), $AUC_{0\text{-}t}$ (ng·h/mL) and $AUC_{0\text{-}\infty}$ (ng·h/mL) was evaluated, and there was no statically significant difference between of two formulations of Rosuvastatin 20 mg ($p \geq 0.05$).

The test/reference ratio, GMRs for the logarithm transformed of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were 103.46% (95.01% - 112.66%), 102.12% (93.38% - 111.67%),

102.09% (93.65% - 111.29%), respectively (Table 3). These values are within the 90% CI acceptance criteria of 80.00% - 125.00% following EMA-Guidelines [25].

Table 3. Pharmacokinetics parameters ln-transformed, 90% CI for the T/R T and R ratio in two Rosuvastatin oral formulations. N = 24.

PK Parameters	GMR (T/R)%	GMR		90% confidence interval	
		Test	Reference	Lower	Upper
C_{max} (ng/mL)	103.46	22.0678	21.3295	95.01	112.66
AUC_{0-t}	102.12	190.8596	186.8978	93.38	111.67
$AUC_{0-\infty}$ (ng·h/mL)	102.09	198.5124	194.4474	93.65	111.29

Data presented as a % mean ln transformed. Cmax: maximum 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; GMR: Geometric mean ratios N = 24; PK: Pharmacokinetics; CI: Confidence interval; ln: natural logarithm.

4. Discussion

Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable *in vivo* performance, i.e. similarity in terms of safety and efficacy [26]. In applications for generic medicinal products according to Directive 2001/83/EC, Article 10(1), the concept of bioequivalence is fundamental. The purpose of establishing bioequivalence is to demonstrate equivalence in biopharmaceutics quality between the generic medicinal product and a reference medicinal product in order to allow bridging of preclinical tests and clinical trials associated with the reference medicinal product. The current definition for generic medicinal products is found in Directive 2001/83/EC, Article 10(2)(b), which states that a generic medicinal product is a product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies [27]. In bioequivalence studies, the plasma concentration time curve is generally used to assess the rate and extent of absorption. C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are the main PK parameters that preset acceptance limits allow the final decision on bioequivalence of the tested products [26].

For many years, the American Heart Association (AHA) and the American College of Cardiology (ACC) have recommended essentials of a healthy diet for the general public and for patients at risk for Atherosclerotic Cardiovascular Disease (ASCVD) [27]. Among lipid-lowering drugs, statins are the cornerstone of therapy, in addition to healthy lifestyle interventions. The intensity of statin therapy is divided into 3 categories: high-intensity, moderate-intensity, and low-intensity. High-intensity statin therapy typically lowers LDL-C levels by ≥50%, moderate-

intensity statin therapy by 30% to 49%, and low-intensity statin therapy by <30%. On the other hand, two categories of triglyceride-lowering drugs, niacin and fibrates, may be useful in some patients with severe hypertriglyceridemia in addition to hypercholesterolemia as seen in mixed dyslipidemia [27]. Rosuvastatin, 5 - 10 mg and 20 - 40 mg is among moderate and high-intensity therapy, respectively, making it very useful in the treatment of patients with high ASCVD risk [27].

The pharmacokinetics of rosuvastatin following single and multiple-dose administration of the drug to healthy volunteers have been investigated in a number of trials [15] [28]. Following multiple oral doses of rosuvastatin (20, 40, and 80 mg) $AUC_{0\text{-}24}$ and C_{max} were essentially dose proportional, time to C_{max} ranged from 3 to 5 h, and the terminal elimination half-life ranged from 13 to 21 h [15].

Generic drugs must be bioequivalent to the original brand name as a prerequisite for marketing approval, because it is theoretically possible that one generic drug may overestimate the pharmacokinetic (PK) parameters of the original and another generic may underestimate these PK parameters; in consequence, these 2 generics may not be bioequivalent between themselves. The result could be loss of efficacy or development of drug-related adverse effects if these generics are interchanged in stable patients [29]. For regulatory reasons and to comply with all the requirements established for the commercialization of generic products [28] [30], it is necessary to carry out bioequivalence studies following international standards (EMA-Guidelines on the investigation of Bioequivalence 01/08/2010), to demonstrate that the R and T formulations are interchangeable [27] [28] and ensure the safety and efficacy of the generic product by testing comparable performance *in vivo* as was carried out in other studies published by our team [30]-[33].

This study was designed to assess the BE of a single 20 mg dose oral tablet formulation of rosuvastatin calcium in healthy Indian volunteers under fasting condition. The bioequivalence of both formulations with respect to the rate and extent of absorption was demonstrated. BE was assessed by measuring the PK parameters; C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$. This is evidenced by the results showing that the 90% CI for ln-transformed ratios of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ fell within the BE acceptance range (80% - 125%).

To other parameters as Tmax h (4.5) to T and (4.25) to R products and Kel (hrs-1) was (0.06 ± 0.030) to T and (0.07 ± 0.03) to R and T1/2 h was (12.20 ± 3.32) to T and (11.70 ± 3.94) to R.

This study demonstrated that rosuvastatin 20 mg was well tolerated among healthy subjects and no adverse events, serious or no serious, were reported.

5. Limitations

We could not assess pharmacokinetics parameters of female volunteers, although the study was open to males and females, only male patients were included. Based on previous studies of the product, no pharmacokinetic differences have been reported between male and female subjects [20].

6. Conclusion

This single-dose study found that the two drugs were bioequivalent, according to the EMA guidelines, the primary pharmacokinetics parameters were within of acceptable range (80.0 - 125.0 percent). Our study demonstrated that test producto Racor® 20 mg (rosuvastatin calcium) tablet should be considered bioequivalent to reference product Crestor® 20 mg (rosuvastatin calcium) tablet, evaluated in healthy male subjects under fasting conditions.

Authors Contributions

JCh, EP and AI performed the statistical analysis, interpretation, writing and revision of the manuscript.

Financial Support and Sponsorship

This study was funded by Laboratorios Leti S.A.V.

Acknowledgements

This study was conducted at the third-party ICBio Clinical Research Pvt. Ltd, located in Vidyaranyapura, Bangalore, India.

Conflicts of Interest

All authors are Industrias Biocontrolled C.A. (Leti Group Company), employees and may hold shares and/or stock options in the company. The authors have no other potential conflicts of interest relevant to this study.

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