Journal of Biosciences and Medicines, 2024, 12, 119-139
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Pharmacokinetics and Bioequivalence Comparison of Two Fixed-Dose Combination of Rosuvastatin/Ezetimibe Formulations: A Randomized, Crossover, Open-Label Study in Healthy Volunteers

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How to cite this paper: Chacón, J.G., Peña, E. and Inatti, A. (2024) Pharmacokinetics and Bioequivalence Comparison of Two Fixed-Dose Combination of Rosuvastatin/Ezetimibe Formulations: A Randomized, Crossover, Open-Label Study in Healthy Volunteers. *Journal of Biosciences and Medicines*, 12, 119-139.
https://doi.org/10.4236/jbm.2024.1210012

Received: September 13, 2024
Accepted: October 13, 2024
Published: October 16, 2024

Abstract

Objective: To evaluate the bioequivalence (BE) of two fixed-dose combination (FDC) formulations of Rosuvastatin and Ezetimibe: Cresadex® EZE 20/10 mg (Abbott Laboratories) as the reference formulation (R), and Racor® Duo 20/10 mg (Laboratorios Leti, S.A.V.) as the test formulation (T). **Method:** A randomized, single-dose, two-period, two-sequence, open-label, crossover design was employed. Subjects received a single oral dose of either the Test or Reference formulation under fasting conditions, with a 12-day washout period between treatments. Male subjects aged 18 - 45 years with normal health and laboratory values were included. Exclusion criteria encompassed any medical conditions, recent surgery, drug or alcohol use, and hypersensitivity to the study drugs. Blood samples were collected at pre-dose and multiple post-dose time points and analyzed using a validated LC-MS/MS method to quantify Rosuvastatin and Ezetimibe concentrations in plasma. Descriptive statistics were used to summarize pharmacokinetic (PK) parameters. ANOVA was conducted to compare the ln-transformed values of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. Schuirmann's two one-sided t-tests were applied to assess bioequivalence (BE). **Results:** The 90% Confidence Intervals for the ln-transformed ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ fell within the acceptance range of 80% to 125%, demonstrating bioequivalence between the Test and Reference formulations. Both formulations were well-tolerated, with no serious adverse events reported. **Conclusions:** The results of this study confirm the bioequivalence of the two tested FDC Rosuvastatin/Ezetimibe formulations: Cresadex® EZE (Abbott Laboratories) and Racor® Duo (Laboratorios Leti, S.A.V.). These findings

endorse the therapeutic interchangeability of these products, providing clinicians with greater flexibility in the treatment of hyperlipidemia.

Keywords

Bioequivalence, Pharmacokinetics, Rosuvastatin, Ezetimibe, FDC

1. Introduction

Rosuvastatin is a synthetic lipid-lowering agent classified as a member of the statin drug class. Its mechanism of action involves the competitive inhibition of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is a rate-limiting enzyme in the biosynthetic pathway for cholesterol production in the liver. It is primarily used to lower cholesterol levels in the blood and reduce the risk of cardiovascular diseases, including heart attacks and strokes [1]. Ezetimibe is a lipid-lowering medication that is primarily used to reduce levels of total cholesterol and low-density lipoprotein (LDL) cholesterol in the blood. Unlike statins, which reduce cholesterol synthesis in the liver, ezetimibe works by inhibiting the absorption of cholesterol from the small intestine. Specifically, it targets the Niemann-Pick C1-Like 1 (NPC1L1) protein, which is responsible for the uptake of cholesterol in the intestines. By blocking this protein, ezetimibe reduces the amount of cholesterol that enters the bloodstream, leading to lower cholesterol levels overall. It is often prescribed in combination with statins for patients who need additional cholesterol reduction [2]. Rosuvastatin is rapidly absorbed after oral administration, with peak plasma concentrations occurring approximately 5 hours after dosing. The drug's bioavailability is around 20%, which is enhanced by taking it with food, is highly protein-bound (approximately 88%) in plasma and distributed throughout the body, including the liver, which is the primary site of its action. The drug is not extensively metabolized by the cytochrome P_{450} enzyme system, which reduces the potential for drug-drug interactions. The elimination half-life of rosuvastatin is approximately 19 hours, allowing for once-daily dosing and it is excreted mainly via the feces (approximately 90% of the dose) and to a lesser extent via urine [3]. Statins metabolized by CYP3A4, such as simvastatin and atorvastatin, are more prone to drug interactions, increasing the risk of muscle toxicity. Conversely, pravastatin and rosuvastatin, which are less dependent on the cytochrome P_{450} system, have fewer interactions, making them safer options for patients at higher risk. While statins can cause mild liver enzyme elevations, these are rarely linked to liver damage. Statins are vital for reducing cardiovascular risk, with serious side effects like rhabdomyolysis being extremely rare. Most side effects, such as myalgia, are mild and reversible. Although statins may raise the risk of diabetes at high doses, their cardiovascular benefits outweigh this risk in high-risk patients. Regular monitoring and personalized treatment are essential to balance efficacy and safety in statin therapy [4]. Ezetimibe is efficiently

absorbed after oral administration and is extensively conjugated to its active metabolite, ezetimibe-glucuronide. Following a single 10 mg dose in fasting adults, the mean C_{max} of ezetimibe ranges from 3.4 to 5.5 ng/mL, achieved within 4 to 12 hours (T_{max}), while ezetimibe-glucuronide reaches a C_{max} of 45 to 71 ng/mL within 1 to 2 hours (T_{max}). The pharmacokinetics of ezetimibe show dose proportionality between 5 and 20 mg. Its absolute bioavailability cannot be determined due to its poor solubility in aqueous media suitable for injection. Ezetimibe is widely distributed throughout the body with a high volume of distribution, and approximately 90% of the drug is bound to plasma proteins. It undergoes extensive hepatic metabolism to form its active glucuronide metabolite but is not significantly metabolized by the cytochrome P_{450} system. Ezetimibe is primarily excreted in the bile, with an elimination half-life of about 22 hours, supporting once-daily dosing [5].

The 2019 ESC/EAS Guidelines for managing hyperlipidemia recommend combining lifestyle changes and medications based on individual risk. Lifestyle modifications include a Mediterranean diet, regular physical activity, smoking cessation, and limiting alcohol. Statins are the first-line treatment to lower LDL cholesterol, with ezetimibe or PCSK9 inhibitors added if needed. LDL targets are <1.4 mmol/L for very high-risk and <1.8 mmol/L for high-risk patients. Risk assessment tools like SCORE guide treatment, especially for those with cardiovascular disease, diabetes, or familial hypercholesterolemia. Regular monitoring of lipid levels and side effects is essential for effective management [6]. Cigarette smoking disrupts lipid metabolism, increasing the risk of atherosclerosis and cardiovascular diseases. It raises total cholesterol (TC) levels and lowers protective high-density lipoprotein cholesterol (HDL-C). Current smokers face a higher risk of developing hyperlipidemia, while quitting smoking reduces this risk, emphasizing the benefits of smoking cessation. Smoking, especially in older individuals with prolonged exposure, is a modifiable risk factor for hyperlipidemia and cardiovascular diseases, highlighting the importance of reducing smoking and managing lipid levels to prevent heart complications [7].

Complementary mechanism of actions of rosuvastatin and ezetimibe resulted in a synergistic therapeutic effect when these drugs were used together [8] [9]. They target different pathways involved in cholesterol regulation. Rosuvastatin reduces cholesterol production in the liver, while ezetimibe reduces cholesterol absorption in the intestine. This complementary action can lead to a more significant reduction in LDL-C levels when used together, compared to either drug alone. This combination can be particularly beneficial for patients who need more aggressive lipid lowering, such as those with high cardiovascular risk or those who do not achieve sufficient LDL-C reduction with statins alone. Using a lower dose of each drug in combination can sometimes reduce the risk of side effects associated with higher doses of statins [10] [11].

Hypertriglyceridemia, commonly linked with conditions like obesity, hypertension, diabetes, and excessive alcohol intake [12], is also a component of metabolic syndrome and poses an independent cardiovascular risk [13]-[15]. While its

predictive value for cardiovascular disease diminishes when accounting for HDL cholesterol, it remains significant [15]. Severe elevations of triglycerides, caused by chylomicron buildup, can lead to acute pancreatitis, with free fatty acids contributing to pancreatic and vascular damage [16]-[19]. Statins, particularly potent ones like rosuvastatin, effectively lower triglyceride levels, especially in high-risk individuals. The mechanism, partially independent of the LDL receptor pathway, likely involves enhanced VLDL uptake by the liver and decreased VLDL production [20].

Regulatory agencies, including the Instituto Nacional de Higiene "Rafael Rangel" in Venezuela, require bioequivalence data to adhere to international standards and guidelines [21] [22]. This ensures alignment with global practices and guarantees that drugs meet established safety and efficacy criteria.

The aim of this study was to assess the bioequivalence (BE) of the fixed-dose combination (FDC) Racor Duo® (Rosuvastatin/Ezetimibe 20/10 mg) film-coated tablet, manufactured by Laboratorios Leti, S.A.V., Guarenas, Venezuela, as the Test product, compared to an equivalent oral dose of the Reference product, Cresadex® EZE (Rosuvastatin/Ezetimibe 20/10 mg) film-coated tablet, manufactured by Laboratorio Franco Colombiano Lafrancol S.A.S, Abbott Laboratories, Colombia, in order to confirm the therapeutic interchangeability of these products.

2. Methods

2.1. Ethical Considerations

This study was conducted ethically in accordance with the principles of the European Medicines Agency, ICH E6 (R2) Good Clinical Practice—Scientific Guideline [22], Indian Council of Medical Research (ICMR) [23], Central Drugs Standard Control Organization, New Drugs & Clinical Trials Rules [24], The World Medical Association (WMA), WMA Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects [25] and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, ICH Harmonised Guideline [26]. The study protocol and the corresponding Informed Consent Form (ICF) were submitted to an Advisory Committee on Ethics (ACE) Independent Ethics Committee on 22 Aug 2023 and approved on 29 Aug 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.

Coated Tablets of Cresadex® EZE 20/10 mg (Rosuvastatin/Ezetimibe), batch 22C753, manufacture and expiration date 27-03-2023 and 30-06-2025, respectively,

Laboratorio Franco Colombiano Lafrancol S.A.S, Colombia, Abbott Laboratories were used as the reference (R) sample and coated tablets of Racor® Duo 20/10 mg (Rosuvastatin/Ezetimibe), batch EP-0822542-01, manufacture and expiration date 16-08-2022 and 16-08-2024, respectively, Laboratorios Leti, S.A.V., Guarenas, Estado Miranda, Venezuela were used as the test (T) sample.

All subjects underwent a screening procedure within 28 days before the first day of their check-in in period I. Upon entering into the study, the subjects were housed in the clinical facility of ICBio clinical research Pvt. Ltd., for at least 10 hours pre-dose until 24 hours post-dose in each period. 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® 9.4 statistical software that ensured balanced allocation to each study period. A washout period of 12 days was maintained between Period-I and Period-II of the study. Male subjects who met the following criteria were included in the study: aged 18 - 45 years, BMI between 18 - 30 kg/m^2, normal clinical history and laboratory values, normal vital signs, chest radiography and 12-lead ECG, negative tests for HIV, Hepatitis B, and Hepatitis C, non-smokers, and able to read and understand the Informed Consent Document. The exclusion criteria included: significant gastrointestinal or blood-forming organ conditions, history of severe infections or major surgery in the past 6 months, minor surgery or fractures within 3 months, significant medical conditions, hypersensitivity to Rosuvastatin or Ezetimibe, positive urine drug tests, recent major illnesses, unusual diet or drug use, and recent participation in other clinical studies. 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 × 20/10 mg coated tablets) of either the Test Product (T) or Reference Product (R) was administered with 240 mL of water at ambient temperature in each period in sequential order from 14:54 on 21 Feb 2024 till 08:40 hours on 23 Feb 2024 (24 subjects) and from 16:49 on 04 Mar 2024 till 08:48 on 06 Mar 2024 (23 subjects), 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 of 20 blood samples (one pre-dose and 19 post-dose) were collected from each subject in each period. The venous blood samples were withdrawn at pre-dose (00.000 hour) and 00.500, 01.000, 01.334, 01.667, 02.000, 02.500, 03.000, 03.500, 04.000, 04.500, 05.000, 06.000, 08.000, 10.000, 12.000, 14.000, 24.000, 48.000, and 72.000 hrs post-dose following drug administration in each

period under yellow monochromatic light. In each period, the pre-dose blood sample was collected within a period of 60 minutes before dosing, post-dose in-house blood samples (*i.e.* up to 24.000 hour post dose) were collected within ± 2 min of the scheduled time and ambulatory blood samples (*i.e.* 48.000 and 72.000 hour post dose) were collected within ±60 min of the scheduled time. All samples were collected in pre-labeled K_2EDTA vacutainers and were centrifuged at 4000 RPM for 10 minutes at 2˚C to 8˚C to separate plasma. All plasma samples were transferred into pre-labeled polypropylene tubes in two aliquots.

2.4. Analytical Procedure

ICBio Clinical Research Private Limited conducted a study to measure concentrations of Rosuvastatin and Ezetimibe in venous plasma using K_2EDTA as an anticoagulant. Analytical instruments were employed, including a Shimadzu Quaternary Pump, an autosampler with a sample cooler (SIL HTC), and a Shimadzu column oven for temperature control, with detection via the LCMS 8050 detector. The analysis was performed using an Ultimasyil C18 column (4.6 × 100 mm, 5 µm) to ensure precise separation of analytes. Plasma samples were processed through solid-phase extraction and analyzed using high-performance liquid chromatography coupled with mass spectrometry (LC-MS/MS). After collection, samples were centrifuged, separated, labeled, and stored at –70˚C ± 15˚C until analysis. Rosuvastatin and Ezetimibe were selectively isolated from 200 µL of plasma using a validated LC-MS/MS method, with internal standards Rosuvastatin D6 and Ezetimibe D4. Samples were processed through HLB Dura cartridges to enhance sensitivity and specificity, followed by LC-ESI-MS/MS analysis for quantification. The method demonstrated high accuracy and precision in measuring Ezetimibe within a linear range of 0.500 to 250.448 ng/mL, evaluated according to SOP No. MV-103-00. Calibration standards and quality control (QC) samples were prepared according to SOP No. MV-107-00, with calibration curve standards stored at –70˚C ± 15˚C and spiked with known Ezetimibe concentrations. The method adhered to strict acceptance criteria, with deviations within 20% for the Lower Limit of Quantification and 15% for other standards, ensuring a strong linear correlation.

2.5. Statistical and Pharmacokinetics Analyses

In the bioequivalence study for rosuvastatin and ezetimibe, statistical and analytical methods were carefully planned to ensure the accuracy and validity of the pharmacokinetic data. 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 and product combination. These statistics included the mean, standard deviation, coefficient of variation, geometric mean, median, and range for each product at each adjusted sampling time point, providing a comprehensive view of the data's distribution and trends. To

analyze the pharmacokinetic parameters, an Analysis of Variance (ANOVA) was performed on the natural logarithm (ln)-transformed values of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for Rosuvastatin, Ezetimibe (unconjugated), and Total Ezetimibe (Ezetimibe + Ezetimibe glucuronide). These parameters were analyzed using a General Linear Model (Proc GLM of SAS®), which accounted for the Fixed Effects of period and treatment, as well as the Random Effect of subjects nested within sequences. Separate ANOVA models were used for each pharmacokinetic parameter, and the main effects were tested at a 0.05 level of significance using the residual error (mean square error/MSE) from the ANOVA model as the error term.

To assess bioequivalence, Schuirmann's Two One-Sided t-tests were employed at a 5% level of significance. These tests compared the average pharmacokinetic parameters for the Test and Reference products, focusing on the ln-transformed values of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for Rosuvastatin, Unconjugated Ezetimibe, and Total Ezetimibe. The 90% Confidence Intervals for the differences between treatments were calculated, providing a statistical range within which the true value of the difference lies with high confidence.

Further analysis involved calculating the Least-Squares Means (LSM) for the ln-transformed pharmacokinetic parameters. The difference between the Test and Reference products was expressed as "Test-Reference," and the ratio of means (T/R) was obtained by taking the anti-log value of the difference. This provided the geometric mean values for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for both Rosuvastatin and Ezetimibe.

Consistent with Schuirmann's two one-sided tests procedure, the 90% Confidence Intervals were expressed by taking the exponential (or anti-log) of the log-transformed data, converting the values back to the normal scale for easier interpretation.

Sample size was based on intra-subject coefficient of variation (CV%) for Rosuvastatin, Unconjugated Ezetimibe, and Total Ezetimibe, as reported in published literatura [5] [27]. The maximum intra-subject CV% was observed for C_{max}, which was approximately 24%.

With an expected coefficient of variation for both C_{max} and AUC not exceeding 26%, and assuming the true ratio of the Test and Reference products would fall between 99% and 101%, the study required at least 21 evaluable subjects to demonstrate bioequivalence with a Power greater than 80% at a 5% level of significance.

To account for potential dropouts or withdrawals, three additional subjects were included, resulting in a total of 24 subjects for the two-treatment, two-period, two-sequence, crossover study design. BE between the Test and Reference formulations of Rosuvastatin/Ezetimibe was demonstrated if the 90% CI fell within the acceptance range of 80% - 125% for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ [28].

2.6. Safety Assessments

Safety of the subjects was evaluated through the assessment of AEs, vital signs and laboratory test (biochemistry, hematology and urinalysis) 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. 23 subjects 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. Table type styles (Table caption is indispensable).

Baseline Characteristics	Total (N = 23)
Sex (Men)	100%
Age (Year)	36.92 ± 4.36
Weight (kg)	73.13 ± 10.17
Height (m)	1.72 ± 0.06
Body Mass Index (kg/m^2)	24.70 ± 2.47

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, Ezetimibe (unconjugated) and Total Ezetimibe (Ezetimibe + Ezetimibe Glucuronide) after administration of Test (T) and Reference (R) products in healthy adult under fasting conditions, in plasma concentration time data using SAS® software version 9.4 (SAS Institute Inc., CARY, USA) (Tables 2-4).

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

ANALITE: Rosuvatatine (N = 23)		
PK Parameters	Test (T)	Reference (R)
C_{max} (ng/mL)	28.77 ± 8.76	32.55 ± 10.91
AUC_{0-t} (ng*hr/mL)	252.50 ± 85.54	286.37 ± 96.36
$AUC_{0-\infty}$ (ng*hr/mL)	267.29 ± 85.82	299.75 ± 97.49
T_{max} (hrs)$^{\#}$	4.50 (1.67 - 5.00)	4.50 (1.00 - 5.00)
K_{el} (hrs^{-1})	0.08 ± 0.03	0.08 ± 0.03
$T_{1/2}$ (hrs)	10.20 ± 5.92	10.51 ± 5.90
AUC_{extrap}	5.88 ± 2.92	4.81 ± 2.72

Data presented as mean ± SE. C_{max}: 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; T_{max}: time to reach C_{max}; K_{el}: elimination rate constant; $T_{1/2}$ time required for plasma. Note: $^{\#}T_{max}$ = Median (range).

Table 3. Pharmacokinetics parameters after a single Ezetimibe 10 mg oral dose of T and R formulations.

ANALITE: Ezetimibe (unconjugated) (N = 23)		
PK Parameters	Test (T)	Reference (R)
C_{max} (ng/mL)	2.07± 1.09	2.28 ± 1.24
$AUC_{0\text{-}t}$ (ng*hr/mL)	31.65 ± 13.67	32.71 ± 14.92
$AUC_{0\text{-}\infty}$ (ng*hr/mL)	43.12 ± 21.24	39.36 ± 15.69
T_{max} (hrs)[#]	4.50 (0.50 - 12.00)	4.50 (1.33 - 14.00)
K_{el} (hrs^{-1})	0.47 ± 0.02	0.06 ± 0.03
$T_{1/2}$ (hrs)	18.02 ± 8.86	14.61 ± 5.02
AUC_{extrap}	23.10 ± 18.63	17.73 ± 11.98

Data presented as mean ± SE. C_{max}: 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; T_{max}: time to reach Cmax; K_{el}: elimination rate constant; $T_{1/2}$ time required for plasma. Note: [#]T_{max} = Median (range).

Table 4. Pharmacokinetics parameters after a single Ezetimibe 10 mg oral dose of T and R formulations.

ANALITE: Total Ezetimibe (ezetimibe + ezetimibe glucuronide) (N = 23)		
PK Parameters	Test (T)	Reference (R)
C_{max} (ng/mL)	158.03± 40.36	166.48 ± 47.59
AUC_{0-t} (ng*hr/mL)	1678.62 ± 526.03	1757.43 ± 576.59
$AUC_{0-\infty}$ (ng*hr/mL)	1769.79 ± 532.51	1840.15 ± 613.72
T_{max} (hrs)[#]	1.83 (0.50 - 4.50)	2.25 (0.50 - 4.50)
K_{el} (hrs^{-1})	0.05 ± 0.02	0.06 ± 0.03
$T_{1/2}$ (hrs)	14.61 ± 4.20	14.35 ± 4.56
AUC_{extrap}	5.65 ± 5.97	4.25 ± 2.87

Data presented as mean ± SE. C_{max}: 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; T_{max}: time to reach C_{max}; K_{el}: elimination rate constant; $T_{1/2}$ time required for plasma. Note: [#]T_{max} = Median (range).

Mean C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, were respectively 28.77 ng/mL, 252.50 ng·h/mL and 267.29 ng/mL for the T formulation and 32.55 ng/mL, 286.37 ng·h/mL and 299.75 ng·h/mL for the R formulation. Median T_{max} was 4.50 h for the T and 4.50 h for the R formulations. Mean plasma concentration versus time curve for each formulation of Rosuvastatine for T and R formulations are presented in **Figure 1** and **Figure 2**.

Mean C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, were respectively 2.07 ng/mL, 31.65 ng·h/mL and 43.12 ng/mL for the T formulation and 2.28 ng/mL, 32.71 ng·h/mL and 39.36 ng·h/mL for the R formulation. Median T_{max} was 4.50 h for the T and 4.50 h for the R formulations. Mean plasma concentration versus time curve for each formulation of Ezetimibe (unconjugated) for T and R formulations are presented in Figure 3 and Figure 4.

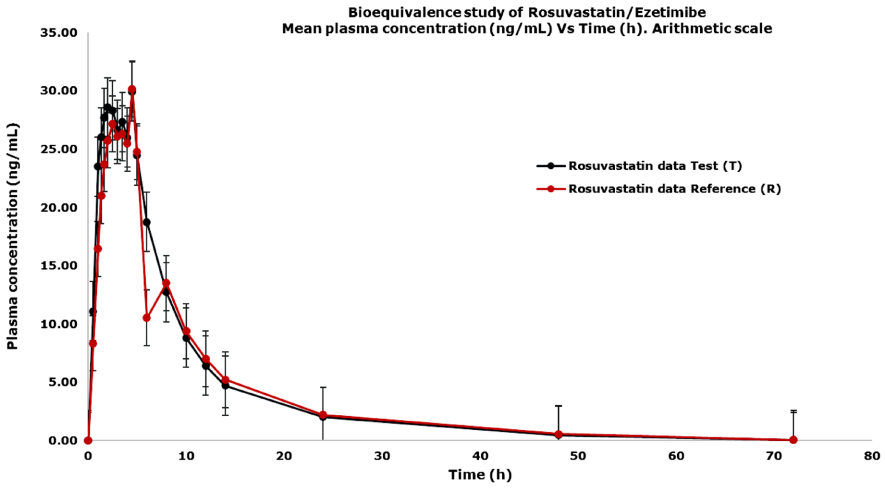

Figure 1. Mean Rosuvastatin 20 mg plasma concentration versus time (h) profile for each formulation is presented in an arithmetic scale, following a single oral dose. Blue line indicates Rosuvastatin (Test product of Laboratorios Leti S.A.V. República Bolivariana de Venezuela), and red line indicates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

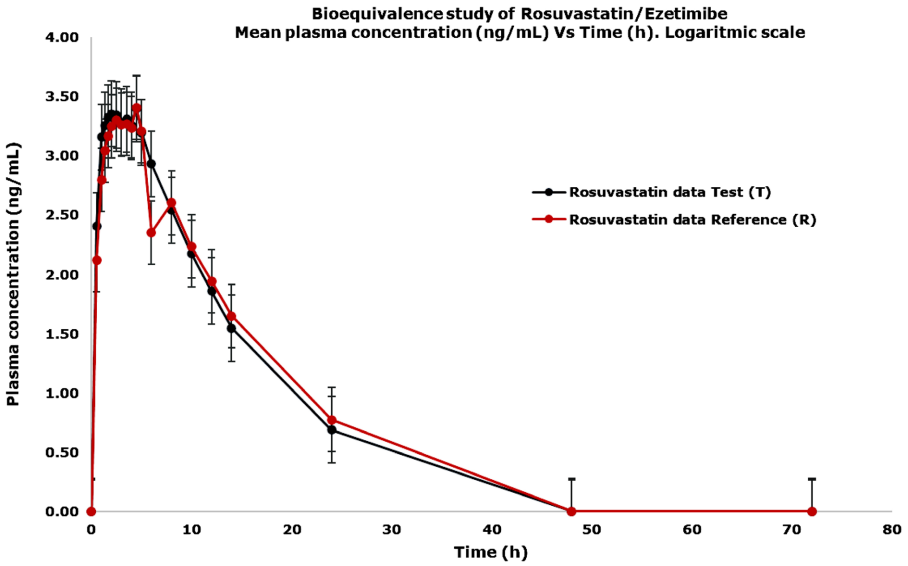

Figure 2. Mean Rosuvastatin 20 mg plasma concentration versus time (h) profile for each formulation is presented in an logarithmic scale, following a single oral dose. Blue line indicates Rosuvastatin (Test product of Laboratorios Leti S.A.V. República Bolivariana de Venezuela), and red line indicates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

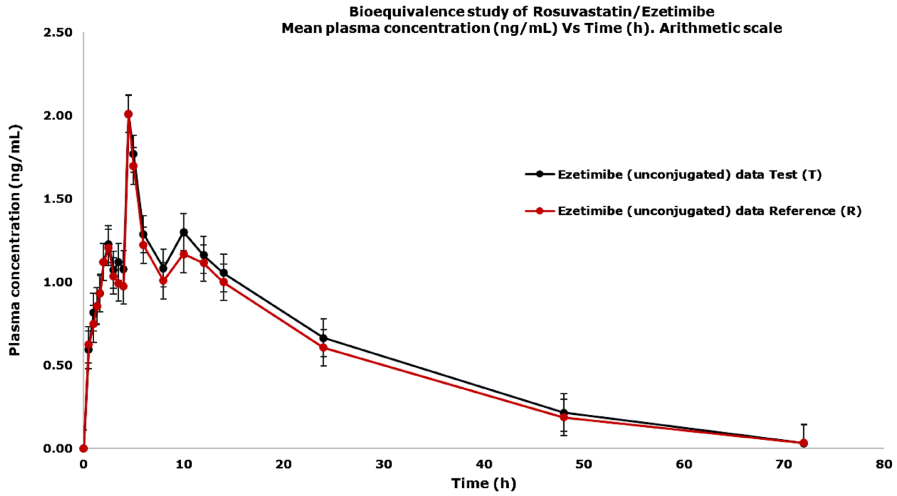

Figure 3. Mean Ezetimibe (unconjugated) plasma concentration versus time (h) profile for each formulation is presented in an arithmetic scale, following a single oral dose. Blue line indicates Ezetimibe (unconjugated) (Test product of Laboratorios Leti S.A.V. República Bolivariana de Venezuela), and red line indicates Ezetimibe (unconjugated) (Reference product of Laboratorio Franco Colombiano Lafrancol S.A.S, Colombia, Abbott Laboratories).

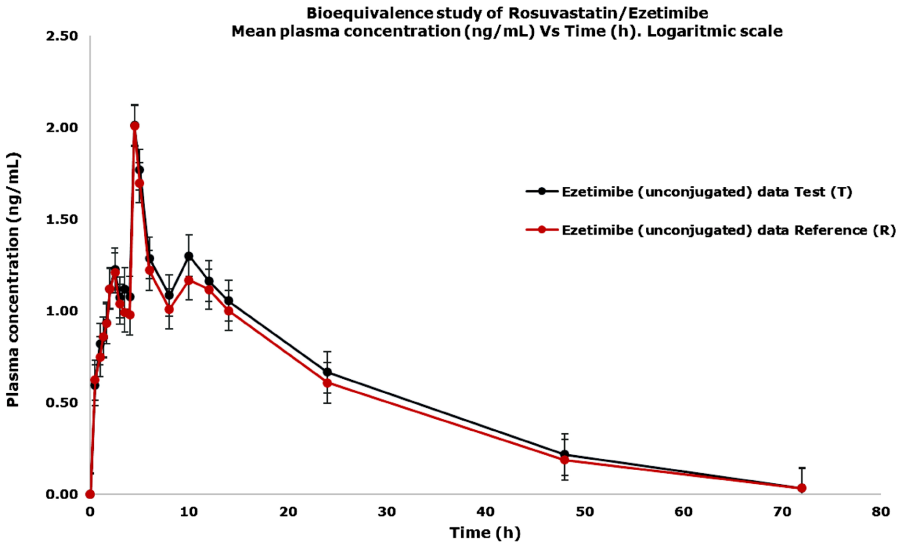

Figure 4. Mean Ezetimibe (unconjugated) plasma concentration versus time (h) profile for each formulation is presented in an logarithmic scale, following a single oral dose. Blue line indicates Ezetimibe (unconjugated) (Test product of Laboratorios Leti S.A.V. República Bolivariana de Venezuela), and red line indicates Ezetimibe (unconjugated) (Reference product of Laboratorio Franco Colombiano Lafrancol S.A.S, Colombia, Abbott Laboratories).

Mean C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, were respectively 158.03 ng/mL, 1678.62 ng·h/mL and 1769.79 ng/mL for the T formulation and 166.48 ng/mL, 1757.43 ng·h/mL and 1840.15 ng·h/mL for the R formulation. Median T_{max} was 1.83 h for the T and 2.25 h for the R formulations. Mean plasma concentration versus time curve for each formulation of Total Ezetimibe (ezetimibe + ezetimibe glucuronide) for T and R formulations are presented in Figure 5 and Figure 6.

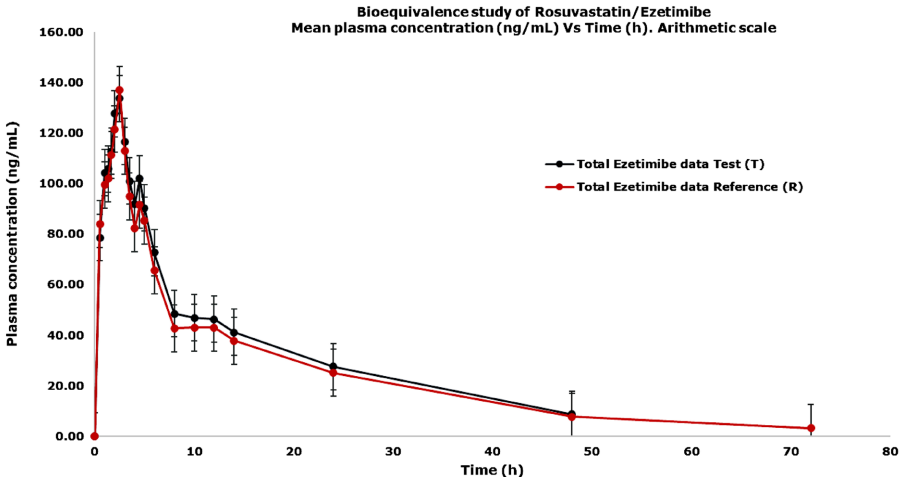

Figure 5. Mean Total Ezetimibe (ezetimibe + ezetimibe glucuronide) plasma concentration versus time (h) profile for each formulation is presented in an arithmetic scale, following a single oral dose. Blue line indicates Total Ezetimibe (ezetimibe + ezetimibe glucuronide) (Test product of Laboratorios Leti S.A.V. República Bolivariana de Venezuela), and red line indicates Total Ezetimibe (ezetimibe + ezetimibe glucuronide) (Reference product of Laboratorio Franco Colombiano Lafrancol S.A.S, Colombia, Abbott Laboratories).

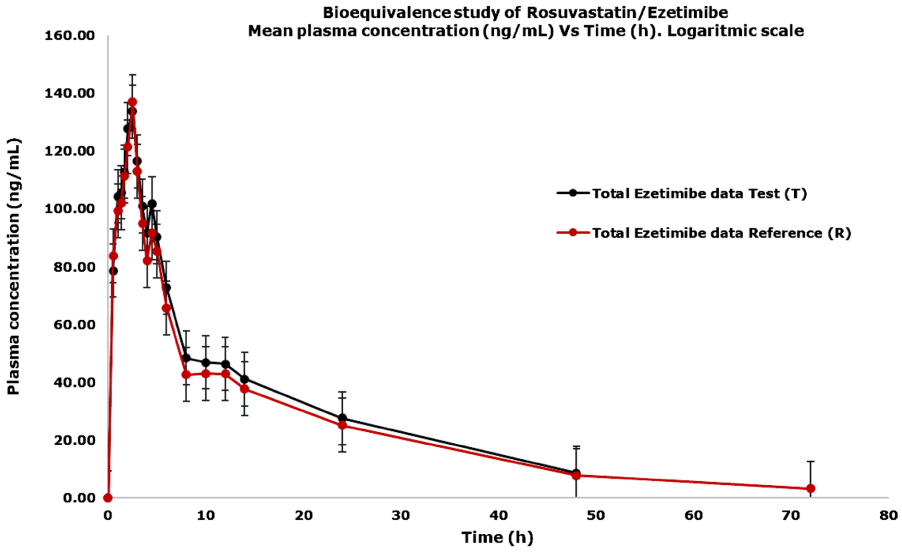

Figure 6. Mean Total Ezetimibe (ezetimibe + ezetimibe glucuronide) plasma concentration versus time (h) profile for each formulation is presented in an logarithmic scale, following a single oral dose. Blue line indicates Total Ezetimibe (ezetimibe + ezetimibe glucuronide) (Test product of Laboratorios Leti S.A.V. República Bolivariana de Venezuela), and red line indicates Total Ezetimibe (ezetimibe + ezetimibe glucuronide) (Reference product of Laboratorio Franco Colombiano Lafrancol S.A.S, Colombia, Abbott Laboratories).

3.3. Bioequivalence

The ANOVA results for log-transformed C_{max} data of Rosuvastatin showed no statistically significant variation for period, treatment, or sequence values between the Test and Reference products. However, the log-transformed AUC_{0-t} and $AUC_{0-\infty}$ data revealed significant variations for treatment values, with no significant

variation for period or sequence. For unconjugated Ezetimibe, the ANOVA results for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ indicated no significant variation for period, treatment, or sequence values. In contrast, for total Ezetimibe (ezetimibe + ezetimibe glucuronide), significant variation was observed for period values, with no variation for treatment or sequence values (Table 5).

For Rosuvastatin, Ezetimibe (unconjugate) and Total Ezetimibe, the Test/Reference ratio, GMRs for the logarithm transformed of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 89.16% (90% CI 80.81% - 98.37%), 88.44% (90% CI 80.74% - 96.87%), 89.45% (90% CI 82.28% - 97.26%); 90.71% (90% CI 80.78% - 101.86%), 97.67% (90% CI 85.95% - 111.00%), 107.81% (90% CI 96.83% - 120.05%) and 95.30% (90% CI 91.32% - 99.45%), 95.60% (90% CI 90.68% - 100.78%), 97.20% (90% CI 92.76% - 101.84%), respectively (Tables 6-8).

These values are within the 90% CI acceptance criteria of 80.00% - 125.00% following EMA-Guidelines [29].

Table 5. Statistical ANOVA results.

p-values	C_{max} (ng/mL)			AUC_{0-t} (ng*hr/mL)			$AUC_{0-\infty}$ (ng*hr/mL)		
	Rosuvastatine	Ezetimibe (unconjugated)	Total Ezetimibe	Rosuvastatine	Ezetimibe (unconjugated)	Total Ezetimibe	Rosuvastatine	Ezetimibe (unconjugated)	Total Ezetimibe
Period	0.59	0.38	0.01	0.47	0.15	0.006	0.50	0.06	0.007
Treatment	0.06	0.16	0.07	0.03	0.75	0.16	0.03	0.24	0.31
Sequence	0.25	0.65	0.62	0.72	0.65	0.94	0.77	0.51	0.91

Table 6. Pharmacokinetics parameters Ln-transformed, 90% CI for the T/R T and R ratio for Rosuvastatin. N = 23.

PK Parameters	GMR (T/R)%	GMR		90% Confidence Interval	
		Test	Reference	Lower	Upper
C_{max} (ng/mL)	89.16	27.51	30.85	80.81	98.37
AUC_{0-t}	88.44	239.93	271.30	80.74	96.87
$AUC_{0-\infty}$ (ng·h/mL)	89.45	255.05	285.12	82.28	97.26

Data presented as a % mean Ln transformed. C_{max}: 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 = 23; PK: Pharmacokinetics; CI: Confidence interval; ln: natural logarithm.

Table 7. Pharmacokinetics parameters Ln-transformed, 90% CI for the T/R T and R ratio for Ezetimibe (unconjugated). N = 23.

PK Parameters	GMR (T/R)%	GMR		90% Confidence Interval	
		Test	Reference	Lower	Upper
C_{max} (ng/mL)	90.71	1.83	2.01	80.78	101.86

Continued

AUC_{0-t}	97.67	28.78	29.47	85.95	111.00
$AUC_{0-\infty}$ (ng·h/mL)	107.81	39.08	36.25	96.83	120.05

Data presented as a % mean Ln transformed. C_{max}: 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 = 23; PK: Pharmacokinetics; CI: Confidence interval; ln: natural logarithm.

Table 8. Pharmacokinetics parameters Ln-transformed, 90% CI for the T/R T and R ratio for Total Ezetimibe (Ezetimibe + Ezetimibe glucuronide). N = 23.

PK Parameters	GMR (T/R)%	GMR		90% Confidence Interval	
		Test	Reference	Lower	Upper
C_{max} (ng/mL)	95.30	153.28	160.85	91.32	99.45
AUC_{0-t}	95.60	1600.93	1674.61	90.68	100.78
$AUC_{0-\infty}$ (ng·h/mL)	97.20	1700.57	1749.61	92.76	101.84

Data presented as a % mean Ln transformed. C_{max}: 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 = 23; PK: Pharmacokinetics; CI: Confidence interval; ln: natural logarithm.

4. Discussion

Fixed-dose combinations drugs (FDCs) have become an essential tool in the management of chronic conditions, including hyperlipidemia, which is characterized by elevated levels of lipids in the blood and significantly increases the risk of cardiovascular diseases, such as heart attack and stroke and typically requires long-term treatment with lipid-lowering medications [30] [31]. FDCs drugs simplify treatment regimens, reducing the number of pills patients must take, which can lead to better adherence. This is particularly important in chronic conditions like hyperlipidemia, where lifelong medication is required and patients are often prescribed multiple medications, which can lead to confusion, forgetfulness, and poor adherence. Studies show that poor adherence to statins and other lipid-lowering drugs can lead to an increased risk of cardiovascular events [32]. FDCs simplify the treatment regimen by combining two or more medications into a single pill. This simplification improves adherence, as patients are more likely to consistently take one pill rather than multiple, leading to better long-term treatment outcomes [33] [34]. By streamlining therapy, FDC drugs address one of the major challenges in patient management: medication nonadherence, which is commonly associated with complex regimens and adverse side effects from higher doses of individual drugs [35] [36]. Additionally, FDC drugs can target multiple mechanisms of lipid regulation, such as combining statins with ezetimibe, which blocks cholesterol absorption in the intestines and reduces cholesterol synthesis in the liver [37] [38]. This multi-

targeted approach results in more effective lowering of LDL-C than monotherapy and also allow for lower doses of each component, reducing the risk of side effects such as muscle-related symptoms, commonly associated with statin use [35] [36]. For instance, combining rosuvastatine with ezetimibe, a drug that reduces cholesterol absorption in the intestines, provides a more comprehensive approach to lowering cholesterol levels. Rosuvastatine work by inhibiting cholesterol synthesis in the liver, while ezetimibe blocks its absorption in the intestines. This dual mechanism results in a greater reduction of low-density lipoprotein cholesterol (LDL-C) than either medication could achieve on its own [39]. By targeting cholesterol from different angles, FDC drugs can enhance the efficacy of treatment and help patients reach their cholesterol goals more effectively. In addition to improving adherence and efficacy, FDC drugs can also reduce treatment costs. By combining two medications into a single pill, FDCs can lower the overall cost of treatment [40] [41]. This is particularly important for patients who require long-term therapy, as the cumulative cost of multiple medications can be significant. Lowering treatment costs can also increase accessibility, making it easier for patients to obtain and adhere to their prescribed therapy. This is especially relevant in managing lifelong conditions like hyperlipidemia, where long-term treatment adherence is critical to reducing the risk of cardiovascular events. Furthermore, FDCs may allow for lower doses of each individual component, which can reduce the risk of side effects [42]. Higher doses of individual medications are often associated with an increased risk of side effects, which can discourage patients from adhering to their prescribed treatment. By using lower doses of each drug in the combination, FDCs can maintain the therapeutic effect while minimizing the risk of adverse reactions. This is particularly beneficial in hyperlipidemia treatment, where side effects such as muscle pain or liver enzyme elevations are common concerns with statin therapy. The ability to reduce side effects while maintaining efficacy makes FDCs a valuable option for many patients.

Regulatory agencies have established several guidelines for the industry regarding the development of fixed-dose combination (FDC) products. The primary guiding principle for the approval of FDC products is the combination rule, as described in FDA and EMA guidelines [43] [44]. This rule states that "two or more drugs may be combined in a single dosage form when each component contributes to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy, as defined in the labeling for the drug."

The efficacy and safety of combination therapy with rosuvastatin and ezetimibe have been demonstrated in several studies on patients with high cardiovascular risk [45]-[48]. The primary benefit of combining rosuvastatin and ezetimibe is their synergistic effect in lowering LDL-C levels. When used together, these drugs provide a more comprehensive approach to managing cholesterol levels compared to monotherapy. Comparing the combination therapy to rosuvastatin alone reveals

the added benefits of ezetimibe, the combination results in greater reductions in LDL-C levels, suggesting that ezetimibe potentiates the lipid-lowering effects of rosuvastatin [49].

In bioequivalence studies, differences between formulations can arise from factors such as sequence, period, formulation, carry-over effects, and individual variability, all of which influence pharmacokinetic profiles [50]. Regulatory agencies like the FDA and EMA [21] [22], provide guidelines to control these factors in BE studies of fixed-dose combination (FDC) products, ensuring observed differences are due to intrinsic formulation properties rather than external influences.

According to these guidelines, several fixed-dose combination (FDC) formulations of rosuvastatin and ezetimibe have been developed and evaluated in bioequivalence studies with the individual administration of each drug [51]-[53]. A bioequivalence study was recently published comparing two fixed-dose combination (FDC) formulations containing rosuvastatin 20 mg and ezetimibe 10 mg in Asian patients, demonstrating that both formulations were bioequivalent [54].

This study was designed to assess the bioequivalence (BE) of two fixed-dose combination (FDC) formulations containing rosuvastatin 20 mg and ezetimibe 10 mg in an oral tablet form in a sample of healthy Indian volunteers under fasting conditions.

The bioequivalence of the products compared in this study, Cresadex® EZE (Abbott Laboratories) as Reference formulation, and Racor® Duo (Laboratorios Leti, S.A.V.) as Test formulation, with respect to the rate and extent of absorption, was demonstrated by measuring the pharmacokinetic (PK) parameters, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

The results of ln-transformed ratios of those parameters showed that the 90% confidence intervals (CI) were within the bioequivalence acceptance range of 80% to 125%, in accordance with international guidelines for bioequivalence studies [28] [55]. Furthermore, the study demonstrated that both FDC formulations were well tolerated by healthy subjects, with no reports of adverse events, either serious or non-serious, therefore no details are available.

5. Limitations

We could not assess pharmacokinetics parameters of female volunteers, although the study was open to both males and females, only male participants were included, as no female volunteers responded to the call for participation. Based on previous studies of the product, no pharmacokinetic differences have been reported between male and female subjects [56].

6. Conclusion

The study concluded that the Test product, Racor-Duo® (Rosuvastatin/Ezetimibe 20/10 mg) film-coated tablet, was bioequivalent to the Reference product, Cresadex® EZE (Rosuvastatin 20 mg/Ezetimibe 10 mg) film-coated tablet. Both formulations demonstrated comparable rates and extents of absorption in healthy adult subjects

under fasting conditions. Additionally, the study monitored safety and tolerability, reporting that the Test product was well-tolerated with no significant adverse events. The bioequivalence, confirmed by pharmacokinetic analysis, indicates that both formulations can be used interchangeably in clinical practice.

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.

References

[1] Davidson, M.H. (2002) Rosuvastatin: A Highly Efficacious Statin for the Treatment of Dyslipidaemia. *Expert Opinion on Investigational Drugs*, **11**, 125-141. https://doi.org/10.1517/13543784.11.1.125

[2] Darkes, M.J.M., Poole, R.M. and Goa, K.L. (2003) Ezetimibe. *American Journal of Cardiovascular Drugs*, **3**, 67-76. https://doi.org/10.2165/00129784-200303010-00007

[3] Crouse, J.R. (2008) An Evaluation of Rosuvastatin: Pharmacokinetics, Clinical Efficacy and Tolerability. *Expert Opinion on Drug Metabolism & Toxicology*, **4**, 287-304. https://doi.org/10.1517/17425255.4.3.287

[4] Ramkumar, S., Raghunath, A. and Raghunath, S. (2016) Statin Therapy: Review of Safety and Potential Side Effects. *Acta Cardiological Sinica*, **32**, 631-639. https://doi.org/10.6515/ACS20160611A

[5] Kosoglou, T., Statkevich, P., Johnson-Levonas, A.O., Paolini, J.F., Bergman, A.J. and Alton, K.B. (2005) Ezetimibe: A Review of Its Metabolism, Pharmacokinetics and Drug Interactions. *Clinical Pharmacokinetics*, **44**, 467-494. https://doi.org/10.2165/00003088-200544050-00002

[6] Mach, F., Baigent, C., Catapano, A., Koskinas, K., Casula, M., Badimon, L., *et al.* (2020) 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: *Lipid Modification to Reduce Cardiovascular Risk*: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *European Heart Journal*, **41**, 111-188. https://doi.org/10.1093/eurheartj/ehz455

[7] Aminullah, Shah, J., Alsubaie, A.S.R., Sehar, B., Khan, F.S., Nawsherwan, *et al.* (2021) Association of Cigarette Smoking with Hyperlipidemia in Male Individuals. *Food and*

Nutrition Sciences, **12**, 937-949. https://doi.org/10.4236/fns.2021.1210069

[8] Ray, K.K., Reeskamp, L.F., Laufs, U., Banach, M., Mach, F., Tokgözoğlu, L.S., *et al.* (2021) Combination Lipid-Lowering Therapy as First-Line Strategy in Very High-Risk Patients. *European Heart Journal*, **43**, 830-833. https://doi.org/10.1093/eurheartj/ehab718

[9] Brown, A.S. (2002) Use of Combination Therapy for Dyslipidemia: A Lipid Clinic Approach. *The American Journal of Cardiology*, **90**, 44-49. https://doi.org/10.1016/s0002-9149(02)02969-7

[10] Cannon, C.P., Blazing, M.A., Giugliano, R.P., McCagg, A., White, J.A., Theroux, P., *et al.* (2015) Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *New England Journal of Medicine*, **372**, 2387-2397. https://doi.org/10.1056/nejmoa1410489

[11] Gagné, C., Bays, H.E., Weiss, S.R., Mata, P., Quinto, K., Melino, M., *et al.* (2002) Efficacy and Safety of Ezetimibe Added to Ongoing Statin Therapy for Treatment of Patients with Primary Hypercholesterolemia. *The American Journal of Cardiology*, **90**, 1084-1091. https://doi.org/10.1016/s0002-9149(02)02774-1

[12] Cowan, L.D., Wilcosky, T., Criqui, M.H., Barrett-Connor, E., Suchindran, C.M., Wallace, R., *et al.* (1985) Demographic, Behavioral, Biochemical, and Dietary Correlates of Plasma Triglycerides. Lipid Research Clinics Program Prevalence Study. *Arteriosclerosis*, **5**, 466-480. https://doi.org/10.1161/01.atv.5.5.466

[13] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001) Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*, **285**, 2486-2497. https://doi.org/10.1001/jama.285.19.2486

[14] Deschamps, E.G., Exsome, C.P., Sánchez, J.V., Flores, B.T., Bastida, S., *et al.* (2007) Metabolic Syndrome Prevalence and Its Association with the Body Mass Index in University Students. *Medicina Clínica*, **129**, 766-769. https://doi.org/10.1157/13113766

[15] Morrison, A. (2008) The Independent Relationship between Triglycerides and Coronary Heart Disease. *Vascular Health and Risk Management*, **5**, 89-95. https://doi.org/10.2147/vhrm.s4311

[16] Li, H., Li, J., Tan, X. and Zhang, Q. (2024) Etitiological Relationship between Hyperlipidemia and Acute Pancreatitis. *Journal of Biosciences and Medicines*, **12**, 45-60. https://doi.org/10.4236/jbm.2024.125005

[17] Navarro, S., Cubiella, J., Feu, F., Zambón, D., Fernández-Cruz, L. and Ros, E. (2004) Hypertriglyceridemic Acute Pancreatitis. Is Its Clinical Course Different from Lithiasic Acute Pancreatitis? *Medicina Clínica*, **123**, 567-570. https://doi.org/10.1016/s0025-7753(04)74599-6

[18] Lloret Linares, C., Pelletier, A.L., Czernichow, S., Vergnaud, A.C., Bonnefont-Rousselot, D., Levy, P., *et al.* (2008) Acute Pancreatitis in a Cohort of 129 Patients Referred for Severe Hypertriglyceridemia. *Pancreas*, **37**, 13-22. https://doi.org/10.1097/mpa.0b013e31816074a1

[19] Coca-Prieto, I., Valdivielso, P., Olivecrona, G., Ariza, M.J., Rioja, J., Font-Ugalde, P., *et al.* (2009) Lipoprotein Lipase Activity and Mass, Apolipoprotein C-II Mass and Polymorphisms of Apolipoproteins E and A5 in Subjects with Prior Acute Hypertriglyceridaemic Pancreatitis. *BMC Gastroenterology*, **9**, Article No. 46. https://doi.org/10.1186/1471-230x-9-46

[20] Sharma, A., Joshi, P.H., Rinehart, S., Thakker, K.M., Lele, A. and Voros, S. (2014)

Baseline Very Low-Density Lipoprotein Cholesterol Is Associated with the Magnitude of Triglyceride Lowering on Statins, Fenofibric Acid, or Their Combination in Patients with Mixed Dyslipidemia. *Journal of Cardiovascular Translational Research*, **7**, 465-474. https://doi.org/10.1007/s12265-014-9559-3

[21] Food and Drug Administration (2014) Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs—General Considerations. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioavailability-and-bioequivalence-studies-submitted-ndas-or-inds-general-considerations

[22] European Medicines Agency (2023) ICH E6 (R2) Good Clinical Practice—Scientific Guideline. EMA/CHMP/ICH/135/1995. https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline#current-version-8263

[23] Indian Council of Medical Research (ICMR) (2017) National Ethical Guidelines for Biomedical and Health Research Involving Human Participants. https://www.indiascienceandtechnology.gov.in/sites/default/files/file-uploads/guidelineregulations/1527507675_ICMR_Ethical_Guidelines_2017.pdf

[24] Central Drugs Standard Control Organization (2019) New Drugs & Clinical Trials Rules. https://cdsco.gov.in/opencms/opencms/en/Acts-and-rules/New-Drugs/

[25] The World Medical Association (WMA) (2013) WMA Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

[26] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (2016) ICH Harmonised Guideline. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

[27] Kanukula, R., Salam, A., Rodgers, A. and Kamel, B. (2021) Pharmacokinetics of Rosuvastatin: A Systematic Review of Randomised Controlled Trials in Healthy Adults. *Clinical Pharmacokinetics*, **60**, 165-175. https://doi.org/10.1007/s40262-020-00978-9

[28] Morais, J.A.G. and do Rosário Lobato, M. (2010) The New European Medicines Agency Guideline on the Investigation of Bioequivalence. *Basic & Clinical Pharmacology & Toxicology*, **106**, 221-225. https://doi.org/10.1111/j.1742-7843.2009.00518.x

[29] CHMP (2014) Committee for Medicinal Products for Human Use. Assessment Report. https://www.ema.europa.eu/en/homepage

[30] Ferri, N., Ruscica, M., Santos, R.D. and Corsini, A. (2023) Fixed Combination for the Treatment of Dyslipidaemia. *Current Atherosclerosis Reports*, **25**, 691-699. https://doi.org/10.1007/s11883-023-01142-x

[31] Catapano, A.L., Farnier, M., Foody, J.M., Toth, P.P., Tomassini, J.E., Brudi, P., *et al.* (2014) Combination Therapy in Dyslipidemia: Where Are We Now? *Atherosclerosis*, **237**, 319-335. https://doi.org/10.1016/j.atherosclerosis.2014.09.026

[32] Klimis, H. and Chow, C.K. (2019) Clinical Consequences of Poor Adherence to Lipid-Lowering Therapy in Patients with Cardiovascular Disease: Can We Do Better? *Heart Asia*, **11**, e011200. https://doi.org/10.1136/heartasia-2019-011200

[33] Wei, Q., Zhou, J., Li, H., Wang, L., Wu, Y., Ma, A., *et al.* (2023) Medication Adherence with Fixed-Dose *versus* Free-Equivalent Combination Therapies: Systematic Review and Meta-Analysis. *Frontiers in Pharmacology*, **14**, Article 1156081. https://doi.org/10.3389/fphar.2023.1156081

[34] Pan, F., Chernew, M.E. and Fendrick, A.M. (2008) Impact of Fixed-Dose Combination

Drugs on Adherence to Prescription Medications. *Journal of General Internal Medicine*, **23**, 611-614. https://doi.org/10.1007/s11606-008-0544-x

[35] Last, A., Ference, J. and Menzel, E. (2017) Hyperlipidemia: Drugs for Cardiovascular Risk Reduction in Adults. *American Family Physician*, **95**, 78-87.

[36] Karr S. (2017) Epidemiology and Management of Hiperlipidemia. *The American Journal of Managed Care*, **23**, S139-S148.

[37] German, C.A. and Liao, J.K. (2023) Understanding the Molecular Mechanisms of Statin Pleiotropic Effects. *Archives of Toxicology*, **97**, 1529-1545. https://doi.org/10.1007/s00204-023-03492-6

[38] Jeu, L. and Cheng, J.W.M. (2003) Pharmacology and Therapeutics of Ezetimibe (SCH 58235), a Cholesterol-Absorption Inhibitor. *Clinical Therapeutics*, **25**, 2352-2387. https://doi.org/10.1016/s0149-2918(03)80281-3

[39] Kim, K., Kim, S., Yoon, Y.W., Rha, S., Hong, S., Kwak, C., *et al.* (2016) Effect of Fixed‐Dose Combinations of Ezetimibe Plus Rosuvastatin in Patients with Primary Hypercholesterolemia: MRS-ROZE (Multicenter Randomized Study of Rosuvastatin and Ezetimibe). *Cardiovascular Therapeutics*, **34**, 371-382. https://doi.org/10.1111/1755-5922.12213

[40] Jahangiri, R., Rezapour, A., Malekzadeh, R., Olyaeemanesh, A., Roshandel, G. and Motevalian, S.A. (2022) Cost-Effectiveness of Fixed-Dose Combination Pill (Polypill) in Primary and Secondary Prevention of Cardiovascular Disease: A Systematic Literature Review. *PLOS ONE*, **17**, e0271908. https://doi.org/10.1371/journal.pone.0271908

[41] Lamy, A., Tong, W., Joseph, P., Gao, P., Huffman, M.D., Roshandel, G., *et al.* (2024) Cost Effectiveness Analysis of a Fixed Dose Combination Pill for Primary Prevention of Cardiovascular Disease from an Individual Participant Data Meta-Analysis. *eClinicalMedicine*, **73**, Article 102651. https://doi.org/10.1016/j.eclinm.2024.102651

[42] Sica, D.A. (2002) Rationale for Fixed-Dose Combinations in the Treatment of Hypertension. *Drugs*, **62**, 443-462. https://doi.org/10.2165/00003495-200262030-00003

[43] Food and Drug Administration, Center for Drug Evaluation and Research (2006) Guidance for Industry: Fixed Dose Combinations, Copackaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV. Food and Drug Administration, Center for Drug Evaluation and Research.

[44] European Medicines Agency, Committee for Medicinal Products for Human Use (2008) Guideline on Fixed Combination Medicinal Products (Draft). European Medicines Agency, Committee for Medicinal Products for Human Use.

[45] Hong, S.J., Jeong, H.S., Ahn, J.C., Cha, D., Won, K.H., Kim, W., *et al.* (2018) A Phase III, Multicenter, Randomized, Double-Blind, Active Comparator Clinical Trial to Compare the Efficacy and Safety of Combination Therapy with Ezetimibe and Rosuvastatin versus Rosuvastatin Monotherapy in Patients with Hypercholesterolemia: I-ROSETTE (Ildong Rosuvastatin & Ezetimibe for Hypercholesterolemia) Randomized Controlled Trial. *Clinical Therapeutics*, **40**, 226-241.E4. https://doi.org/10.1016/j.clinthera.2017.12.018

[46] Moon, J.S., Park, I.R., Kim, S.S., Kim, H.S., Kim, N.H., Kim, S.G., *et al.* (2023) The Efficacy and Safety of Moderate-Intensity Rosuvastatin with Ezetimibe versus High-Intensity Rosuvastatin in High Atherosclerotic Cardiovascular Disease Risk Patients with Type 2 Diabetes Mellitus: A Randomized, Multicenter, Open, Parallel, Phase 4 Study. *Diabetes & Metabolism Journal*, **47**, 818-825. https://doi.org/10.4093/dmj.2023.0171

[47] Yang, Y., Lee, S., Kim, B.S., Cho, Y., Cho, H., Cho, K.I., *et al.* (2017) Combination

Therapy of Rosuvastatin and Ezetimibe in Patients with High Cardiovascular Risk. *Clinical Therapeutics*, **39**, 107-117. https://doi.org/10.1016/j.clinthera.2016.11.014

[48] Kim, W., Yoon, Y.E., Shin, S., Bae, J., Hong, B., Hong, S.J., *et al.* (2018) Efficacy and Safety of Ezetimibe and Rosuvastatin Combination Therapy versus Those of Rosuvastatin Monotherapy in Patients with Primary Hypercholesterolemia. *Clinical Therapeutics*, **40**, 993-1013. https://doi.org/10.1016/j.clinthera.2018.04.015

[49] Ballantyne, C.M., Weiss, R., Moccetti, T., Vogt, A., Eber, B., Sosef, F., *et al.* (2007) Efficacy and Safety of Rosuvastatin 40 Mg Alone or in Combination with Ezetimibe in Patients at High Risk of Cardiovascular Disease (Results from the EXPLORER Study). *The American Journal of Cardiology*, **99**, 673-680. https://doi.org/10.1016/j.amjcard.2006.10.022

[50] Sato, M. and Narukawa, M. (2015) Factors Affecting Intrasubject Variability of PK Exposure: Absolute Oral Bioavailability and Acidic Nature of Drugs. *International Journal of Clinical Pharmacology and Therapeutics*, **53**, 955-962. https://doi.org/10.5414/cp202399

[51] Kang, W.Y., Seong, S.J., Ohk, B., Gwon, M., Kim, B.K., Na, S., *et al.* (2017) Pharmacokinetics and Bioequivalence of a Rosuvastatin/Ezetimibe Fixed-Dose Combination Tablet versus Single Agents in Healthy Male Subjects. *International Journal of Clinical Pharmacology and Therapeutics*, **56**, 43-52. https://doi.org/10.5414/cp203026

[52] Di, Y., Wang, Z., Jia, C., Xie, X., Yang, S., Wang, W., *et al.* (2023) A Bioequivalence Study of Ezetimibe/Rosuvastatin Fixed Dose Combination (10 Mg/10 Mg) versus the Individual Formulations Taken Concomitantly. *Advances in Therapy*, **40**, 2205-2216. https://doi.org/10.1007/s12325-023-02439-8

[53] Migoya, E.M., Bergman, A., Hreniuk, D., Matthews, N., Yi, B., Roadcap, B., *et al.* (2006) Bioequivalence of an Ezetimibe/Simvastatin Combination Tablet and Coadministration of Ezetimibe and Simvastatin as Separate Tablets in Healthy Subjects. *International Journal of Clinical Pharmacology and Therapeutics*, **44**, 83-92. https://doi.org/10.5414/cpp44083

[54] Leong, C.W., Yee, K.M., Rani, T.A., Lau, K.J., Ahmad, S., Amran, A., *et al.* (2024) Pharmacokinetics and Bioequivalence of Fixed-Dose Combination of Simvastatin and Ezetimibe Tablets: A Randomized, Crossover, Open-Label Study in Healthy Volunteers. *Clinical Pharmacology in Drug Development*, **13**, 938-946. https://doi.org/10.1002/cpdd.1411

[55] CHMP (2010) Guideline on the Investigation of Bioequivalence. https://www.ema.europa.eu/en/homepage

[56] Torimoto, K., Okada, Y., Mori, H., Hajime, M., Tanaka, K., Kurozumi, A., *et al.* (2013) Efficacy of Combination of Ezetimibe 10 Mg and Rosuvastatin 2.5 mg versus Rosuvastatin 5 mg Monotherapy for Hypercholesterolemia in Patients with Type 2 Diabetes. *Lipids in Health and Disease*, **12**, Article No. 137. https://doi.org/10.1186/1476-511x-12-137