FINAL VERSION OF STUDY REPORT

COMPARATIVE RANDOMIZED, SINGLE DOSE, TWO-WAY CROSSOVER OPEN-LABEL STUDY TO DETERMINE THE BIOEQUIVALENCE OF ATORVASTATIN FROM ATORVASTATIN 40 MG TABLET (SAJA PHARMACEUTICALS) AND LIPITOR ® 40 MG TABLET (GODECKE, PARKE DAVIS), AFTER ORAL ADMINISTRATION OF 40 MG TO HEALTHY ADULTS UNDER FASTING CONDITIONS

CONTRACT RESEARCH ORGANIZATION:	*International Pharmaceutical Research Center (IPRC)*
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SPONSOR:	*SAJA Pharmaceuticals, Saudi Arabia*
ADDRESS:	*Saudi Arabia*
DRUG IDENTIFICATION:	*Atorvastatin*
DRUG INDICATION:	*Hyper lipidemia*
SPONSORS SIGNATORY REPRESENTATIVE:	*Bassam El-Wadii, Plant Manager* *SAJA Pharmaceuticals, Saudi Arabia*
IPRC PROTOCOL CODE:	*ATO-T005*
IPRC STUDY CODE:	*ATO-SAJ-T1205/402*
STUDY INITIATION:	*Protocol Approval: 04/01/2006*
STUDY COMPLETION:	*Report Issue: 24/04/2007*
STUDY PERIODS:	*Screening commencement: 17/01/2006* *Period I: 23/01/2006* *Period II: 06/02/2006*

IPRC INVESTIGATORS:

Principal Investigator: *Naji M. Najib, B.Sc. Pharm., Ph.D.,*
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Clinical Investigator: *Usama Harb, M.D.,*
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International Pharmaceutical Research Center, Jordan.

THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH INTERNATIONAL CONFERENCE OF HARMONIZATION (ICH) GOOD CLINICAL PRACTICE (GCP) GUIDELINES ADOPTED BY THE EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS (EMEA).

ESSENTIAL DOCUMENTS AND RECORDS WERE ALL ARCHIVED ACCORDING TO INTERNATIONAL PHARMACEUTICAL RESEARCH CENTER (IPRC) INTERNAL PROCEDURES FOR AUTHORIZED DIRECT ACCESS.

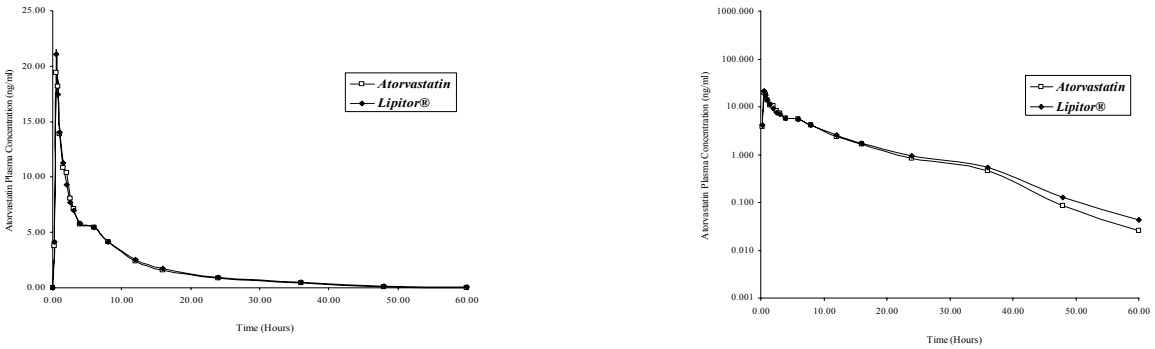
THIS FINAL REPORT WAS GENERATED IN REFERENCE TO INTERNATIONAL CONFERENCE OF HARMONIZATION (ICH) GUIDELINES ADOPTED BY THE EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS (EMEA) FOR STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS

STUDY SYNOPSIS

SPONSOR: *SAJA Pharmaceuticals*	
GENERIC NAME *Atorvastatin*	**TABLE REFERENCE PART (S)**
TEST PRODUCT *Atorvastatin*	**1. ETHICS** **2. INTRODUCTION** **3. INVESTIGATION**
REFERENCE PRODUCT *Lipitor®*	
STUDY TITLE	*Comparative Randomized, Single Dose, Two-Way Crossover Open-Label Study To Determine The Bioequivalence Of Atorvastatin From Atorvastatin 40 mg Tablet (SAJA Pharmaceuticals) And Lipitor ® 40 mg Tablet (Godecke, Parke Davis), After Oral Administration Of 40 mg To Healthy Adults Under Fasting Conditions*
IPRC PROTOCOL CODE	*ATO-T005*
IPRC STUDY CODE	*ATO-SAJ-T1205/402*
INSTITUTIONAL REVIEW BOARD	*Institutional Review Board of IPRC, Jordan.*
OBJECTIVES	*To investigate the single-dose bioequivalence of SAJA Pharmaceuticals (TEST product, Atorvastatin 40 mg atorvastatin per tablet) and Godecke, Parke Davis. (REFERENCE product, Lipitor® 40 mg atorvastatin per tablet) in healthy adults under fasting conditions.*
INVESTIGATORS	**Principal Investigator:** *Naji M. Najib, B.Sc. Pharm., Ph.D., International Pharmaceutical Research Center, Jordan.* **Clinical Investigator:** *Usama Harb, M.D., International Pharmaceutical Research Center, Jordan.*
DOSAGE REGIMEN	*Treatment A (TEST Product): Single-Dose, one tablet of Atorvastatin (40 mg atorvastatin per tablet). Batch No. 05F032TV, Exp. Date: 06/07* *Treatment B (REFERENCE Product): Single-Dose, one tablet of Lipitor® (40 mg atorvastatin per tablet) Batch No. 0495054, Exp. Date: 04/07*
CLINICAL LABORATORY	*IPRC clinical laboratory*

SPONSOR: *SAJA Pharmaceuticals*	
GENERIC NAME *Atorvastatin*	**TABLE REFERENCE PART(S)**
TEST PRODUCT *Atorvastatin*	**3. INVESTIGATION (*CONTINUED*)** **4. STUDY SUBJECTS**
REFERENCE PRODUCT *Lipitor®*	
STUDY SUBJECTS	*40 subjects, selected randomly from the Jordan population, were enrolled in the study, to investigate the bioequivalence in 36 subjects.*
DEMOGRAPHIC DATA (N=36)	*Age: 24 ± 4.27 year* *Height: 173 ± 5.86 cm* *Weight: 74 ± 8.48 Kg*
ADMISSION AND CONFINEMENT	*Subjects were admitted the night before Study Drug Administration, supervised for at least 10 hours of overnight fasting, and confined until collecting the 24-hour sample.*
DRUG ADMINISTRATION	*Each subject received an oral dose of the assigned formulation, according to a randomisation scheme, administered with 240 ml water.*
STUDY PERIODS	*Screening: 17/01/2006* *Enrollment: 22/01/2006* *Period I: 23/01/2006* *Period II: 06/02/2006* *First Sample: 23/01/2006* *Last sample: 08/02/2006*
WASHOUT PERIOD	*Fourteen days from the first study drug administration.*
ANCILLARY ASSESSMENT	*Safety/adverse events, laboratory tests, physical examination, vital signs*
BLOOD SAMPLING SCHEDULE	*Nineteen blood samples were drawn at 0.00 (Two pre- dose +), 0.25, 0.50, 0.75, 1.00, 1.50, 2.00 , 2.50, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, 24.00 , 36.00, 48.00 and 60.00 hours (post-dose). The total volume of blood draws did not exceed 314 ml.*
BLOOD SAMPLES HANDLING	*The blood samples for atorvastatin were collected in heparinized tubes, centrifuged and the resulting plasma samples were immediately stored at –20°C until analysed.*
CLINICAL SAMPLES STORAGE	*Atorvastatin plasma samples were stored under a nominal temperature of –20°C until analysed.*
BIOANALYTICAL METHODOLOGY	*LC/MS/MS, with LLOQ = 0.5 ng/ml*

SPONSOR: *SAJA Pharmaceuticals*	
GENERIC NAME *Atorvastatin*	**TABLE REFERENCE PART(S)**
TEST PRODUCT *Atorvastatin*	**5. SAFETY EVALUATION** **6. RESULTS AND BIOEQUIVALENCE EVALUATION** **7. DISCUSSION AND CONCLUSION**
REFERENCE PRODUCT *Lipitor®*	
TOLERANCE	*Both treatments were well tolerated*
SURROGATE PARAMETERS	*Drug plasma levels to indicate clinical activity*
PRIMARY PHARMACOKINETIC PARAMETERS	C_{max}, $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$
SECONDARY PHARMACOKINETIC PARAMETERS	K_e, t_{max}, $t_{½e}$, and ($AUC_{0\rightarrow t}$/ $AUC_{0\rightarrow\infty}$) %
CONFIDENCE INTERVALS (PARAMETRIC METHOD)	*Confidence Intervals for the log-transformed Test/Reference Ratios of:* C_{max} 95.27 (82.98 – 109.36) % $AUC_{0\rightarrow t}$ 94.86 (90.28 – 99.67) % $AUC_{0\rightarrow\infty}$ 93.89 (89.42 – 98.58) %
CONCLUSIONS	*Point estimates and the 90% Confidence Intervals for the log-transformed ratios (TEST/REFERENCE) were within the accepted limits of 80.00% - 125.00% for $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$ and within 75.00% - 133.00% for $C_{max,}$. Therefore, the bioequivalence of SAJA Pharmaceuticals (Atorvastatin tablet); and Godecke, Parke Davis (Lipitor® tablet), can be concluded.*



Atorvastatin mean plasma concentration after single dose administration of one tablet of Atorvastatin 40 mg atorvastatin per tablet (TEST Product) and one tablet of Lipitor® 40 mg atorvastatin per tablet (REFERENCE Product) to 36 healthy subjects.

Final Report Issuance Date	***24 April 2007***

INVESTIGATORS STATEMENT

COMPARATIVE RANDOMIZED, SINGLE DOSE, TWO-WAY CROSSOVER OPEN-LABEL STUDY TO DETERMINE THE BIOEQUIVALENCE OF ATORVASTATIN FROM ATORVASTATIN 40 MG TABLET (SAJA PHARMACEUTICALS) AND LIPITOR ® 40 MG TABLET (GODECKE, PARKE DAVIS), AFTER ORAL ADMINISTRATION OF 40 MG TO HEALTHY ADULTS UNDER FASTING CONDITIONS

Principal Investigator Approval:

I hereby state that, I assessed the consistency of the report contents from the scientific point of view, and to the best of my knowledge, the reports scientific basis, results and conclusions were in agreement with published literature.

Signature:_____ Date:_____/_____/_____

N.Najib. B.Sc. Pharm.Ph.D.,
Principal Investigator,
International Pharmaceutical Research Center

Sponsors approval:

I hereby state that, I assessed the consistency of the report contents from the scientific point of view, and to the best of my knowledge, the reports scientific basis, results and conclusions were in agreement with published literature.

Signature:_____ Date:_____/_____/_____

Bassam El-Wadii, Plant Manager
SAJA Pharmaceuticals, Saudi Arabia

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ANOVA	Analysis Of Variance
AUC	Area Under the plasma concentration-time Curve
$AUC_{0\rightarrow t}$	Area Under the plasma concentration-time Curve from zero (0) hours to time (t)
$AUC_{0\rightarrow \infty}$	Area Under the plasma concentration-time Curve from zero (0) hours to infinity (∞)
BUN	Blood Urea Nitrogen
C_{last}	Last Quantifiable Concentration
C_{max}	Maximal Plasma Concentration
CRF	Cases Report Form
EMEA	The European Agency for the Evaluation of Medicines for Human Use.
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IPRC	International Pharmaceutical Research Center
IRB	Institutional Review Board
K_e	Elimination rate constant
LLOQ	Lower Limit of Quantification
Log	Logarithm
QAU	Quality Assurance Unit
SAE	Serious Adverse Events
Serious ADR	Serious Adverse Drug Reactions
SOP	Standard Operating Procedure
SGOT	Serum Glutamic Oxalate Transaminase
SGPT	Serum Glutamic Pyruvate Transaminase
t_{max}	Time point of maximal plasma concentration
$t_{1/2e}$	Elimination half life
USP-NF	The United States Pharmacopeia–The National Formulary

LIST OF DEFINITIONS[1]

Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) Product.

Approval (in relation to Institutional Review Boards)

The affirmative decision of the Institutional Review Board (IRB) that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Bioavailabilty

It is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.

Bioequivalence

It is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar conditions in an appropriately designed study.

Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

Clinical Trial/Study Report

A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report.

Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

Direct Access

Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects identities and sponsor's proprietary information.

Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Informed Consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Pharmaceutical Equivalents

Defined as drug products that contain identical amounts of the identical active drug ingredient, i.e. the same salt or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the same inactive ingredients, and that meet the identical compendial or other applicable standard of identity, strength, quality and purity, including potency and, where applicable, content uniformity, disintegration times and/ or dissolution rates

Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the report Guideline the term protocol refers to protocol and protocol amendments.

Protocol Amendment

A written description of a change(s) to or formal clarification of a protocol.

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose results in death, is life-threatening, - requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect

Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the Laboratoires and at medico-technical departments involved in the clinical trial).

Standard Operating Procedures (SOPs)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

Subject Identification Code

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

1. ETHICS

1.1. Institutional Review Board

The Institutional Review Board of IPRC, Amman, Jordan was dedicated to endorse the ethical conduct of the study and to approve the protocol. The Board is constituted and operates in accordance with the principles and requirements described in Guidelines on Research Involving Human Subjects. The Study Protocol was reviewed by the IRB of IPRC. The approval for the Study Protocol was given on January 04,2006 as demonstrated in appendix 1.2.

1.2. Ethical Conduct of the Study

This research was carried out in accordance with conditions stipulated by International Clinical Research guidelines, enunciated in the Declaration of Helsinki resolved in Helsinki in 1964 and amended in Scotland, 2000[2]; updated in Washington, note added in Tokyo 2004 and the ICH harmonised tripartite guideline regarding Good Clinical Practice (GCP) adopted by the European Agency for the Evaluation of Medicinal Products [3]. In addition, all local regulatory requirements were adhered to, in particular those which afford greater protection to the safety of the study participants.

1.3. Informed Consent

Before screening procedures, the IPRC staff informed the subjects, in non technical terms, of the objectives, dates, drugs, diet, potential risks and general activities during the clinical part of the study. The informed consent forms were carefully read before signing. Any questions were discussed in detail with the IPRC staff. Special emphasis was placed on the adherence of subjects to the Study Protocol and on the possible adverse events. At the end of consent procedures, each subject received a copy of the Informed Consent Form, a sample of which is enclosed in Appendix 1.4.

1.4. Justification of the Study

Since drug formulation plays a key role in drug absorption, thus variations are expected from one formula to another for the same particular drug. Moreover, drug pharmacodynamics can be affected by its pharmacokinetics, which is invariably influenced by drug product formulation. All these necessitate the need for a biometric tool to prove the drug pharmaceutical equivalence or bioequivalency [4, 5, 6]. Accordingly, the interchangeable use of bioequivalent products is justified and should afford the same therapeutic efficacy.

2. INTRODUCTION

This study was performed to investigate the bioequivalence of atorvastatin between a TEST Product *Atorvastatin* (40 mg atorvastatin per tablet; SAJA Pharmaceuticals, Saudi Arabia), and REFERENCE Product *Lipitor*® (40 mg atorvastatin per tablet; Godecke, Parke Davis, Germany). The Study Protocol called for 36 healthy volunteers plus 1-4 alternates. The subjects received one tablet of *Atorvastatin* (40 mg atorvastatin per tablet) and one tablet of *Lipitor*®, (40 mg atorvastatin per tablet) in a randomised fashion with a washout period of 14 days. Thirty five healthy volunteers plus three alternates completed the crossover. The bioanalysis of clinical plasma samples was accomplished by LC/MS/MS method, which was developed and validated in accordance with International guidelines[1,7,8] at IPRC. Pharmacokinetic parameters, determined by standard non-compartmental methods, and ANOVA statistics were calculated using Kinetica™ 2000 Statistical Software. The significance of a sequence effect was tested using the subjects nested in sequence as the error term. The 90% confidence intervals for the ratio (or difference) between the test and reference product pharmacokinetic parameters of AUC $_{0\rightarrow t}$, AUC $_{0\rightarrow\infty}$ and C_{max} were calculated and found to be within the confidence limits of 80.00-125.00% for $AUC_{0\rightarrow t}$ AUC $_{0\rightarrow\infty}$ and within 75.00 – 133.00 %. for C_{max}.

In conclusion, the study demonstrated that the TEST Product, *Atorvastatin* tablet (SAJA Pharmaceuticals, Saudi Arabia), 40 mg atorvastatin per tablet, is bioequivalent to the REFERENCE Product, *Lipitor*® tablet (Godecke, Parke Davis, Germany) 40 mg atorvastatin per tablet following an oral dose of 40 mg, as summarized by Tables 1 and 2 below.

This report is issued in consensus with the ICH guidelines concerning the Structure and Content of the Clinical Study Reports adopted by EMEA.[9]

Table 1 Bioequivalence Confidence Intervals of atorvastatin (*Atorvastatin* tablet the TEST Product versus *Lipitor*® tablet the REFERENCE Product)

Pharmacokinetic Parameter	90% Confidence intervals of parametric means		
	Point estimate %	Lower Limit %	Upper Limit %
C_{max}	95.27	82.98	109.36
$AUC_{0\rightarrow t}$	94.86	90.28	99.67
$AUC_{0\rightarrow\infty}$	93.89	89.42	98.58

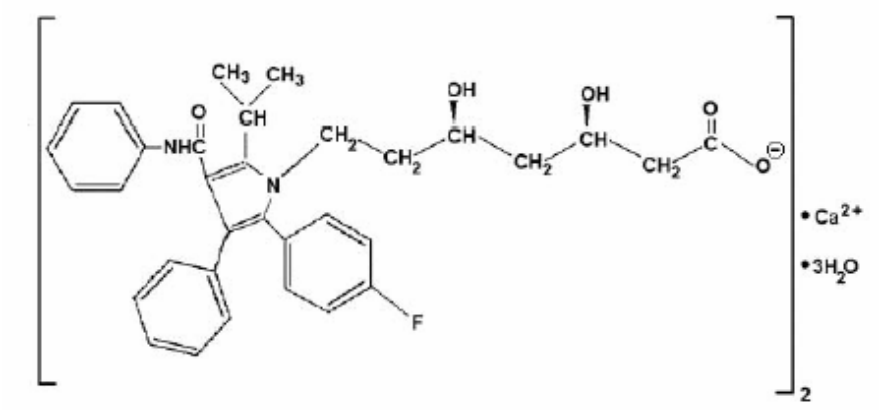
Table 2 Pharmacokinetics Parameters of atorvastatin (*Atorvastatin* Tablet the TEST Product versus *Lipitor*® Tablet the REFERENCE Product)

Pharmacokinetic Parameter	Treatment (Mean ± SD)	
	TEST Product	REFERENCE Product
C_{max} (ng/ml)	23.38 ± 13.62	24.75 ± 16.15
$AUC_{0\rightarrow t}$ (ng.h/ml)	97.83 ± 85.36	101.51 ± 75.21
$AUC_{0\rightarrow\infty}$ (ng.h/ml)	110.32 ± 87.24	113.27 ± 76.79
t_{max} (h)	0.88 ± 0.96	0.69 ± 0.41
$t_{½e}$ (h)	10.14 ± 5.00	11.37 ± 5.07
$AUC_{0\rightarrow t}/AUC_{0\rightarrow\infty}$%	88.83 ± 5.52	87.74 ± 6.64
K_e (1/h)	0.0853 ± 0.04	0.0737 ± 0.03

2.1. Chemistry

Atorvastatin calcium is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Atorvastatin calcium is [R-(R*,R*)]-2-(4-fluorophenyl)-β,γ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-lH-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)2Ca\cdot 3H_2O$ and its molecular weight is 1209.42.. Its structural formula is:



Atorvastatin calcium

2.2.Clinical Pharmacology and Mechanism of Action

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions.

Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

2.3.Pharmacokinetics

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1-2 hours. Extent of absorption increases in proportion to atorvastatin dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%,

respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration

Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20-30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

2.4.Therapeutic Uses

Atorvastatin is indicated:

3. As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.
4. As an adjunct to diet for the treatment of patients with elevated serum TG levels .
5. For the treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet.
6. To reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

2.5 Adverse Events

The following adverse events were reported, regardless of causality assessment in patients treated with atorvastatin in clinical trials. The events in *italics* occurred in ≥ 2% of patients and the events in plain type occurred in <2% of patients.

> ***Body as a Whole:*** *Chest pain,* face edema, fever, neck rigidity, malaise, photosensitivity reaction.
> ***Digestive System:*** *Nausea,* gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphasia, melena, gum hemorrhage.
> ***Respiratory System:*** *Bronchitis, rhinitis,* pneumonia, dyspnea, asthma, epistaxis.
> ***Nervous System:*** *Insomnia, dizziness,* paresthesia, somnolence, amnesia, neuropathy, depression
> ***Musculoskeletal System:*** *Arthritis,* leg cramps, myasthenia.
> ***Skin and Appendages:*** Pruritus, contact dermatitis, dry skin, sweating, acne, hair loss.
> ***Urogenital System:*** *Urinary tract infection,* urinary frequency, cystitis, impotency.
> ***Special Senses:*** Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss.
> ***Cardiovascular System:*** Palpitation, vasodilatation, migraine, postural hypotension, , arrhythmia, angina pectoris
> ***Metabolic and Nutrtional Disorders:*** *Peripheral edema,* hyperglycemia, gout, weight gain, hypoglycemia.
> ***Hemic and Lymphatic System:*** anemia thrombocytopenia.

3. INVESTIGATION

3.1.Investigators and Study Administrative Structure

The clinical part of the study was performed in the IPRC clinical site (Amman, Jordan) under the supervision of Professor Naji Najib, the Principal Investigator; and Usama Harb, M.D., Clinical Investigator. The calculations of the pharmacokinetics and statistical evaluation of data was performed at IPRC. Data entry was performed by Dalia Saleh (B.Sc. Pharm.), and results were authorized by Professor Naji Najib (B.Sc. Pharm., Ph.D.). Bioanalysis was performed at IPRC using the in-house developed and validated [7,8] method. The final report of the study was authored by Dalia Saleh (B.Sc. Pharm.). The Quality Assurance Unit (QAU) unit was entirely involved in auditing and checking, throughout the study conduction and completion. The curriculum vita of each investigator and co-investigator is enclosed in appendix 1.5.

3.2. Study Objectives

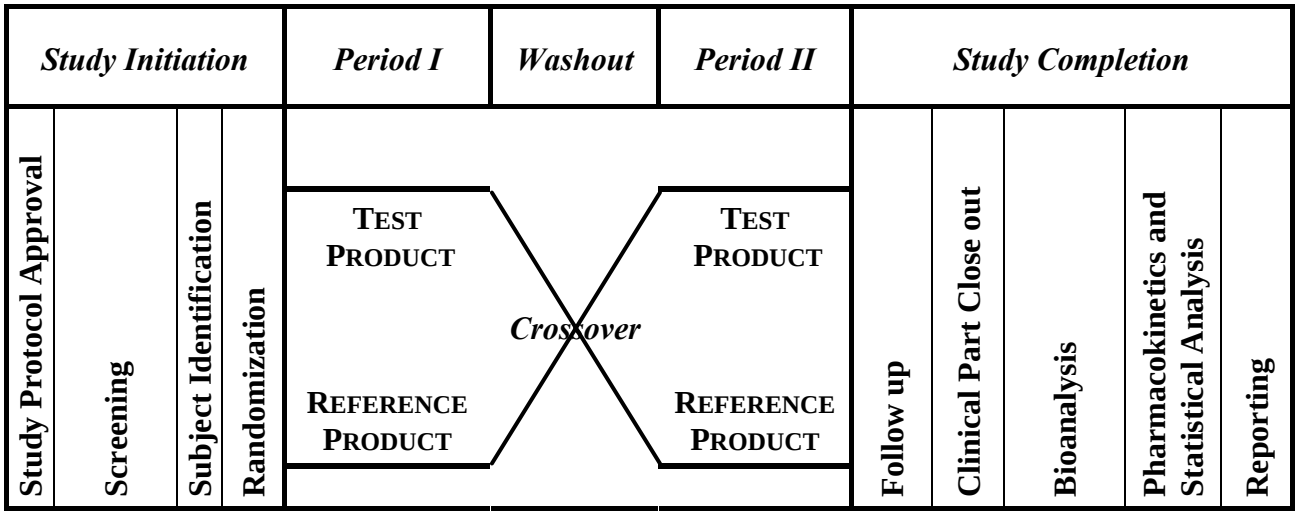
In this study, the bioavailability of a single dose of 40 mg atorvastatin of SAJA Pharmaceuticals (*Atorvastatin* 40 mg atorvastatin per tablet) and Godecke, Parke Davis (*Lipitor*® 40 mg atorvastatin per tablet), were compared under fasting conditions. Bioequivalence was investigated by determining the 90% confidence limits for the log-transformed ratio (TEST Product/REFERENCE Product) for the bioequivalence parameters (C_{max}, $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$), while other pharmacokinetic parameters of K_e, $t_{½e}$, t_{max} and percent ($AUC_{0\rightarrow t}$ /$AUC_{0\rightarrow\infty}$) were reported. The influence of sequence, product and period effect was tested by ANOVA.

3.3. Investigational Plan

This study was a single Center, open-label, randomised, single-dose study with two-way crossover design to compare the bioavailability of atorvastatin between two products, in 36 healthy, adult, subjects.

The study was conducted according to ICH GCP guidelines adopted by EMEA. For all the steps carried out in this study, IPRC has written standard operating procedures (SOPS) of which IPRC personnel have control of the training on and the use of the SOPs. The Institutional Review Board of IPRC, Amman, Jordan, reviewed the Study Protocol and approval was given on 04/01/2006. (See appendix 1.2. "Approval of the Institutional Review Board"). The clinical part of the study was initiated at the IPRC clinical site, by the first screening examination on 17/01/2006. After the screening examination, subjects were sequenced according to a pre-assigned randomization plan. The first administration of the study drug, as well as, the first blood collection for drug analysis took place on 23/01/2006. A washout period of 14 days between the two Study Drug administrations was allowed. The last study drug administration took place on 06/02/2006, while the last blood collection for drug analysis took place on 08/02/2006. Blood sampling per each Study Period was carried out as per sampling schedule.

Figure 1 Study Design and Plan



The clinical study site facilities were designed and equipped appropriately to accommodate all running activities of the study. A detailed description of the study site facilities is mentioned under "Description of the study site facilities".

Bioanalysis of atorvastatin was performed by LC/MS/MS method at IPRC. Bioanalytical method validation results are provided within appendix 1.8 "Bioanalytical Report".

3.4. Rationale of Study Design

Bioequivalence evaluation is usually carried out by comparing the *in vivo* rate and extent of drug absorption of a test and reference formulation in healthy subjects. In a standard *in vivo* bioequivalence study design, study participants received test and reference products on separate occasions, in single dose, with random assignment to the two possible sequences of product administration. Samples of plasma were analyzed for drug concentrations, and pharmacokinetic parameters were obtained from the resulting concentration-time curves. These pharmacokinetic parameters were then analyzed statistically to determine if the test and reference products yielded comparable values. Standard statistical methodology based on the two one-sided tests procedure to determine whether average values for pharmacokinetic parameters measured after administration of the test and reference products are comparable. This procedure involves the calculation of a 90% confidence interval for the ratio (or difference) between the test and reference product pharmacokinetic variable averages. The limits of the observed confidence intervals were within a predetermined range for the ratio (or difference) of the product averages. The determination of the confidence interval range and the statistical level of significance based on parametric (normal-theory) standard noncompartmental procedures was employed for the analysis of pharmacokinetic data derived from *in vivo* bioequivalence studies. An analysis of variance (ANOVA) was performed on the pharmacokinetic parameters to assess the effect of variables (subject (sequence), subject, period and formulation) on the study outcome. On the basis of these considerations, a single-dose, two-treatment, two-period, two-sequence crossover bioequivalence study on healthy normal subjects was adopted. The study was conducted in preplanned scheme, as depicted in Table 3 below.

Table 3 Study Schematic.

Procedure	Study Period *			
	Screening †	Period I	Period II	Follow-up#
Subject Identification	✓	✓	✓	✓
Informed Consent ♣	✓			
Selection Criteria ‡	✓			
Demographic Data	✓			
Medical History	✓			
Physical Examination	✓			✓
Vital Signs	✓	✓	✓	✓
Hepatitis B	✓			
Haematology	✓			
Biochemistry	✓			
Urinalysis	✓			
Study Drug Administration		✓	✓	
Check for Other Medication	✓	✓	✓	
Blood Sampling for Pharmacokinetics		✓	✓	
Check for Adverse Effect		✓	✓	✓

* *There was a washout Period of 14- day between the two administrations of the study's drug.*
† *Between 30 days and approximately 24 hours before first study's drug administration in Period I*
‡ *To be eligible for participation in the study, the subjects must meet all the selection criteria before the first study's drug administration in Period I is established.*
♣ *Before screening examination, the subject has to sign an informed consent form (ICF).*
Follow- up is to be done within at least 24 hours of the last blood sample

3.5. Selection of Study Population

For participation in the study, subjects had to meet the selection criteria outlined in the Study Protocol. Volunteers were informed, by IPRC representative, about the aim of the study and any potential risk associated with the study. Volunteers signed a written Informed Consent statement after which they were run in the study, and they were free to withdraw at any time during the course of the study.

3.5.1. Study Subjects Demography

The following demographic data for each subject were obtained:

- Age, height, weight, date of birth, race, medical history and vital signs.
- Complete physical examination and neurological assessment.
- Urine analysis and Blood (hematology, biochemistry and serology).

3.5.2. Inclusion criteria

To be eligible for participation in the study, subjects must meet all of the following criteria before their enrolment in the study.

4.7.1. Inclusion criteria

1. Age 18 to 45 years, inclusive.
2. Body weight within 15% of ideal weights for height and weight (Table of "Desirable Weights of Adults", Metropolitan Life Insurance Company Statistical Bulletin, 1983)
3. Medical history, vital signs and physical examination (including neurological assessment) without evidence of clinically significant deviation from normal medical condition, performed not longer than two weeks before the initiation of the clinical study.
4. Results of laboratory tests are within the normal range or with a deviation that is not considered clinically significant by both the Clinical Investigator and the Principal Investigator. (Laboratory tests are performed not longer than one month before the initiation of the clinical study).
5. Subject does not have allergy to the drugs under investigation.

3.5.3. Exclusion criteria

1. Medical history, vital signs and/or physical examination with evidence of clinically significant deviation from normal medical condition.
2. Results of laboratory tests, which are clinically significant.
3. Acute infection within one week preceding first Study Drug administration.
4. History of drug or alcohol abuse.
5. Subject is a heavy smoker (more than 10 cigarettes per day).
6. Subject does not agree not to take any prescription or non-prescription drugs within two weeks before first study drug administration until the end of the study.
7. Subject does not agree not to take any vitamins taken for nutritional purposes within two days before first study drug administration until the end of the.
8. Subject is on a special diet (for example subject is vegetarian)
9. Subject consumes large quantities of alcohol or beverages containing methylxanthines e.g. caffeine, tea, cola, chocolate etc.
10. Subject does not agree not to consume any beverages or foods containing alcohol 48 hours prior to Study Drug administration until donating the last sample in each respective period.

11. Subject does not agree not to consume any beverages or foods containing methyl-xanthines e.g. caffeine (coffee, tea, cola, chocolate etc.) 48 hours prior to the Study Drug administration of either Study Period until donating the last sample in each respective Period.

12. Subject does not agree not to consume any beverages or foods containing grapefruit 7 days prior to first Study Drug administration until donating the last sample in each respective Period.

13. Subject has a history of severe diseases which have direct impact on the study

14. Participation in a bioequivalence study or in a clinical study within the last 2 months before first Study Drug administration.

15. Subject intends to be hospitalized within 3 months after first Study Drug administration.

16. Subjects who, through completion of this study, would have donated more than 500 ml of blood in 14 days, or 750 ml of blood in 30 days, 1000 ml in 90 days, 1250 ml in 120 days, 1500 ml in 180 days, 2000 ml in 270 days, 2500 ml of blood in 1 year.

3.6. Subjects Identification

On screening subjects were identified solely by their initials. On admission for period I participating subjects were assigned numbers in sequential order. The subjects retained their numbers for the duration of the study. For subsequent data processing and reporting, subjects were identified only by using the numbers they were assigned and their initials.

3.7. Case Report Form Note

All data of the clinical part of the study was documented in case report forms (CRFs) by the staff of the IPRC. The Principal Investigator checked correct completion of the case report forms. A sample CRF is enclosed in appendix 1.3. IPRC performed quality assurance of case report forms' data entry by comparison with source records.

3.8. Confinement

According to the Study Protocol in each study period the subjects were admitted to the study site in the evening before study drug administration on Study Day 1 of each study period and confined until the 24-hour blood sample was collected. Subjects returned to donate the rest of samples.

3.9. Removal of Subjects from Study

Each subject had the right to withdraw from the study at any time without jeopardy or prejudice. The Principal Investigator and the Clinical Investigator have the right to discontinue the subjects' participation if they felt it is necessary, for any reason including adverse events or failure to comply with the study protocol.

When a subject withdrew from the study, the reasons were stated on the Case Report Form and a final evaluation of the subject was performed.

Subjects' withdrawal may be divided into three groups:

Withdrawal group 1:

withdrawal after screening procedures have been performed but before Study Drug administration in Study Period I.

Withdrawal group 2:

withdrawal after Study Drug administration in Study Period I but before Study Drug administration in Study Period II.

Withdrawal group 3:

withdrawal after Study Drug administration in Study Period II but before last sample collection in Study Period II.

3.10. Dietary Restrictions, Standardized Diet and Fluid Intake

No consumption of alcohol, beverages or foods containing methylxanthines, e.g. caffeine (coffee, tea, cola, cocoa, chocolate, etc.) was permitted for the subjects 48 hours prior to the study's drugs administration until the collection of last blood sample of the respective study period. In addition, the consumption of any beverages or foods containing grapefruit was prohibited one week before first study's drugs administration and through out the entire study.

Food and fluid-intake was identical in both study periods; starting from the dinner served 10 hours before study's drugs administration on study day -1 until the end of confinement. Meals were standardized in composition and amount in both periods. The subjects were not allowed to consume any additional beverages or foodstuffs other than those provided through out the period of confinement. The subjects received their standardized meals at the following times:

Table 4 Standardized Diets served during the study

Study Day	Standardized Diet	Time Received
-1	Dinner	Finished at least 10 hours before the scheduled time of study drug administration in the morning of study day 1
1	Lunch	4 hours after study drug administration
1	Dinner	12 hours after study drug administration

Details of the diet's composition are provided in appendix 2.6.

No excessive fluid-intake (>120 ml of water per hour) was allowed from 1 to 10 hours prior to dosing. From 1 hour before study's drugs administration to 2 hours after, no fluid intake was allowed apart from the 240 ml of water used for the administration. 2 hours following the study's drugs administration, the subjects were allowed to have not more than 120 ml of water per hour.

3.11. Study Drug Administration

On Study Day 1 of each Study Period, the study drugs were administered according to a randomization plan (see appendix 1.6.) The administration of the Study Drugs was documented in the drug administration forms.

Study Drugs were administered by the clinical staff of IPRC as follows:

Treatment A: One tablet of *Atorvastatin*, TEST Product, 40 mg atorvastatin per tablet, was given with 240 of ml water. Water was at room temperature and was measured with a 250 ml cylinder.

Treatment B: One tablet of *Lipitor*®, REFERENCE Product, 40 mg atorvastatin per Tablet, was given with 240 ml of water. Water was at room temperature and was measured with a 250 ml cylinder.

3.12. Identity of Study Medications

Identification	TEST Product Treatment A	REFERENCE Product Treatment B
Brand Name	*Atorvastatin*	*Lipitor*®
Dosage Form	Tablet	Tablet
Strength	40 mg atorvastatin per tablet.	40 mg atorvastatin per tablet.
Manufacturer	SAJA Pharmaceuticals, Saudi Arabia	Godecke, Parke Davis, Germany
Batch No.	05F032TV	0495054
Expiry Date	06/07	04/07

3.13.Assignment of Study's Subjects and Randomisation

The study was randomised as a two-way two-sequence crossover design. Administration was done according to a plan of randomisation (see appendix 1.6).

3.14.Times of Dosing

The first administration of the Study Drugs took place on 23/01/2006. And the last study's drugs administration took place on 06/02/2006. The study's Drugs administration took place between 08:00 and 08:38 for group I and between 08:00 and 08:36 for group II in the morning of Study Day 1 of both Periods. For detailed information about date and time of study drug administration, see appendix 2.5.

3.15.Treatment Compliance

Visual inspection of the subject's hands and mouth was immediately done after the study's drugs administration to ensure that the subject did swallow the drug.

3.16. Physical Activities after Drug Intake

After the study's drugs administration, the subjects remained ambulatory. Their activity was restricted to talking, watching television or reading until the 4-hour blood collection (except for the scheduled time of blood sampling and going to the toilet which is allowed only two hours post dosing). The blood collection rooms and the toilets were on the same floor. The study personnel took great care to ensure that the physical activity of the subjects was identical in Study Day 1 of each Study Period.

3.17. Prior and Concurrent Medication

According to the study's protocol, no prescription or non-prescription medication was to be taken starting 2 weeks before the first study's drugs administration until the end of the study (collection of the last sample of Period II). None of the subjects consumed any drug throughout the study.

3.18.Clinical Laboratory:

IPRC clinical laboratory, Amman, Jordan, performed the safety laboratory investigations (hematology, biochemistry, urinalysis and serology).

3.19. Description of Study Facilities

The clinical site of IPRC is set in two floors of the IPRC building. Each floor is designed to withstand a full scale study completely sealed from the remaining running activities in the IPRC building. The following rooms were used for this study:

Room for pre-study examinations

All pre-study examination took place in a separate room. This room was equipped with a blood pressure monitor, stethoscope, scale….etc and all the necessary materials. All equipment necessary for handling of the blood and urine samples were available.

Clinical Investigator's Office

Here the Clinical Investigator carries out all the physical examinations of the study's subjects whither on screening or follow up.

Room for the administration of the Study Drugs, vital signs and blood collection
In this room, cannula insertion, study's drug administration, as well as, blood collection was carried out. For each sampling time a nurse was delegated for the responsibility of blood collection at that time. The volunteers were called into the room at the assigned collection time and had their blood drawn. Similarly, a nurse was delegated for taking the vital signs at the assigned time and the volunteers were called in to have their vital signs taken. A clock and all equipment necessary for blood collection from the volunteers were available.

Pharmacy
The study's drug was stored in sealed containers in a closed cabinet in the pharmacy located on the 1st floor of the IPRC building. All necessary storage conditions were taken into account in handling and dispensing of the study's drug. Temperature and humidity monitoring were carried out as appropriate. A data logger placed in the pharmacy records the temperature and humidity level there.

Emergency Room (ER)
Located on the second floor and equipped with all the necessary equipment needed in case of an emergency and drugs necessary for treatment of serious adverse events were available.. In addition to IPRC's ER, IPRC has signed an agreement with the Arab Medical Centre for the use of its available emergency unit to handle emergencies that may occur during the study. The Arab Medical Centre emergency unit supervisor has been well informed of the study's nature, including the study's drug

(strength and dose to be used), number of involved subjects and dates of admission to each study period.

Subject's Rooms
Here subjects spend most of the study's time, watching T.V. or reading except when they are called for blood sampling or vital signs measurments.

Kitchen
Food was prepared and stored in the kitchen situated in the basement. The meals were always stored in locked meal trolleys. The kitchen was equipped with a cupboard for the dishes, an oven, fridge, freezer, and a washbasin with running hot and cold water for cleaning up.

Dormitories
Each of the two floors of the clinical site has one room furnished with all the necessary beds, sheets, linen and pillows. The study's subjects slept in these rooms.

Dining rooms
One room was used for dining. This room is on the same floor of the study.

Bathrooms/ Toilets
Subjects could use any of the four bathrooms present (but preferably the one in their respective room for good control on study subjects). These contained a washbasin, toilet and a shower facility.

3.20. Collection and Handling of Blood Samples for Analysis

In the morning of Study Day 1 of each study period and before study's drugs administration, a cannula was inserted into the subject's forearm vein and remained there until the 24-hour blood sample was collected.

The volume of blood taken for determination of atorvastatin in plasma was 8 ml per sample. The following blood samples for the analysis of atorvastatin in plasma were collected Immediately before (2 × 8 ml) at 0.00 (pre- dose) and at 0.25, 0.50, 0.75, 1.00, 1.50, 2.00 , 2.50, 3.00, 4.00, 6.00, 8.00, 12.00, 16.00, 24.00 , 36.00, 48.00 and 60.00 hours (1 × 8 ml) after administration of Study's Drugs. The number of blood collections for drug analysis was 19 samples in each Study Period.

Blood samples were collected into tubes containing heparinised as an anticoagulant (Dispo™, AFMA, Jordan), slightly shaken and centrifuged at approximately 3500 r.p.m for 10 minutes. After centrifugation, plasma samples were transferred directly into a two light protected plain plastic tubes (Dispo™, AFMA, Jordan). These samples were immediately stored at the study site in a freezer at a nominal temperature of -20°C. The label of the collecting tubes had the study's code number, subject number, study period and the designated sample number. It did not contain information that would allow identifying the given treatment. This assured that the analysts at IPRC analyzed the samples blindly. The total amount of blood loss during the whole study (including blood for laboratory tests) did not exceed 314 ml:

[((1 × 8 ml + 1 × 8 ml for pre-dose samples) + (17 × 8 ml for subsequent samples)) × 2], including 10 ml for screening.

3.21 Bioanalytical Drug Determination Methodologies

An LC/MS/MS assay was developed at the IPRC for the determination of atorvastatin in human plasma. Samples from the first 36 subjects (who completed both periods of the study and fulfilled the balanced design) were analysed. The bioanalytical method was validated according to international guidelines. Details of the validation of the assay procedure are given in appendix 1.8. "Bioanalytical Report".

3.22.Data Quality Assurance

The IPRC's quality assurance procedures were implemented to assure the built-in quality system. All data entry was done by the trained staff of IPRC and checked by the QAU personnel. All procedures were performed according to the internal IPRC approved SOPs with the results being documented and reported.

Deliberately, all in-use manuals were archived by the QAU. All notebooks used to document results were issued and approved by the QAU serially, and ultimately reserved in the QAU. Logbooks were audited internally by the IPRC QAU personnel during the internal audit of both the clinical part and the analytical part of the study. All laboratory (clinical and analytical) results were checked and their source documents retained by the QAU. Source document verification was done by the QAU after each data entry. Instrumental outputs after calculations were checked by the QAU personnel. Necessary actions were taken and corrective and/or preventive measures were recommended. A report after each audit period was delivered to the IPRC management. Report of audits were followed up and reserved by the QAU. The QAU implements an internal quality system to keep all essential records related to the study guaranteeing the appropriate authorized direct access and traceability of data with utmost confidentiality. All audit trails were enabled within the operated software.

3.23.Pharmacokinetic Calculations

Under the direction of Professor N. Najib, the pharmacokinetic parameters of atorvastatin were estimated using standard non-compartmental methods. The maximal plasma concentration (C_{max}) and the time to peak plasma concentration (t_{max}) of atorvastatin were taken directly from the measured data.

The area under the plasma concentration-time curve ($AUC_{0\rightarrow t}$) was calculated from measured data points from time of administration to time of last quantifiable concentration (C_{last}) by the linear trapezoidal rule.

The area under the plasma concentration-time curve extrapolated to infinity ($AUC_{0\rightarrow\infty}$) was calculated according to the following formula:

$$AUC_{0\rightarrow\infty} = AUC_{0\rightarrow t} + C_{last} / [Ln\ (2) / t_{½e}],$$ where C_{last} is the last quantifiable concentration.

The ratio $AUC_{0\rightarrow t} / AUC_{0\rightarrow\infty}$ as a percent was determined as an indicator for the adequacy of sampling time.

The elimination half-life ($t_{½e}$) was calculated as:

$t_{½e}$ = Ln (2) / (-b), where b was obtained as the slope of the linear regression of the Ln-transformed plasma concentrations versus time in the terminal Period of the plasma curve.

The pharmacokinetic calculations were performed on a Pentium MMX MHz Computer using the computer program Kinetica™ 2000.

3.24.Statistical Analysis [10, 11, 12]

Statistical analysis was performed by using the Kinetica ™ 2000 program, with the aid of Microsoft® Excel (2002).

3.24.1. Confidence Intervals

The extent of absorption is determined by $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$. The rate of absorption is indetermined by C_{max}. For the parametric analysis of bioequivalence for Ln-transformed data, the acceptance boundaries were set at 80.00-125.00% for $AUC_{0\rightarrow t}$ AUC $_{0\rightarrow\infty}$ and within 75.00 – 133.00 %. for $C_{max.}$

A multiplicative model with respect to the untransformed bioequivalence parameters was selected. A logarithmic transformation of the original data was used. Under the assumption of a logarithmic normal distribution, a parametric approach recommended by Steinijans and Diletti based on the inclusion of the shortest 90% confidence interval in the bioequivalence range was adopted [5].

3.24.2.Analysis of Variance (ANOVA)

An analysis of variance (ANOVA) tested for sequence, period, subject (sequence) and treatment effects was used. ANOVA was performed on $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, C_{max}, t_{max}, $t_{1/2e}$, K_e, Ln $AUC_{0\rightarrow t}$, Ln $AUC_{0\rightarrow\infty}$ and Ln C_{max}.

A multiplicative linear model was used for the two-way crossover design:

$Yijk = \log (Xijk) = \mu + Gk\ Sik + Pj + F (j , k) + eijk,$

Where,

Yijk = is a pharmacokinetic parameter of the ith subject ($i = 1 , 2 , \ldots n_k$) in the sequence ($k = 1, 2, \ldots k$) for the jth period ($j = 1 , 2 , \ldots p$).

μ : is the overall mean.

Gk : is the fixed effect of the kth sequence .

Sik: is the random effect of the ith subject in the kth sequence .

Pj : is the fixed effect of the jth period.

F (j, k): is the fixed effect of the formulation in the kth sequence, which is administered at the jth period.

And,

eijk : is the (within subject) random error in observing Yijk .

It was assumed that {Sik} and {eijk} are mutually independent and normally distributed with mean zero and variances σs^2 and σe^2.

3.25. Data Tabulation, Descriptive Statistics and Diagrammatic Data Presentation

All results and diagrammatic data presentation are depicted in "Tables and Figures Referred to but not included in the Text"

4. STUDY SUBJECTS

4.1. Disposition of Subjects

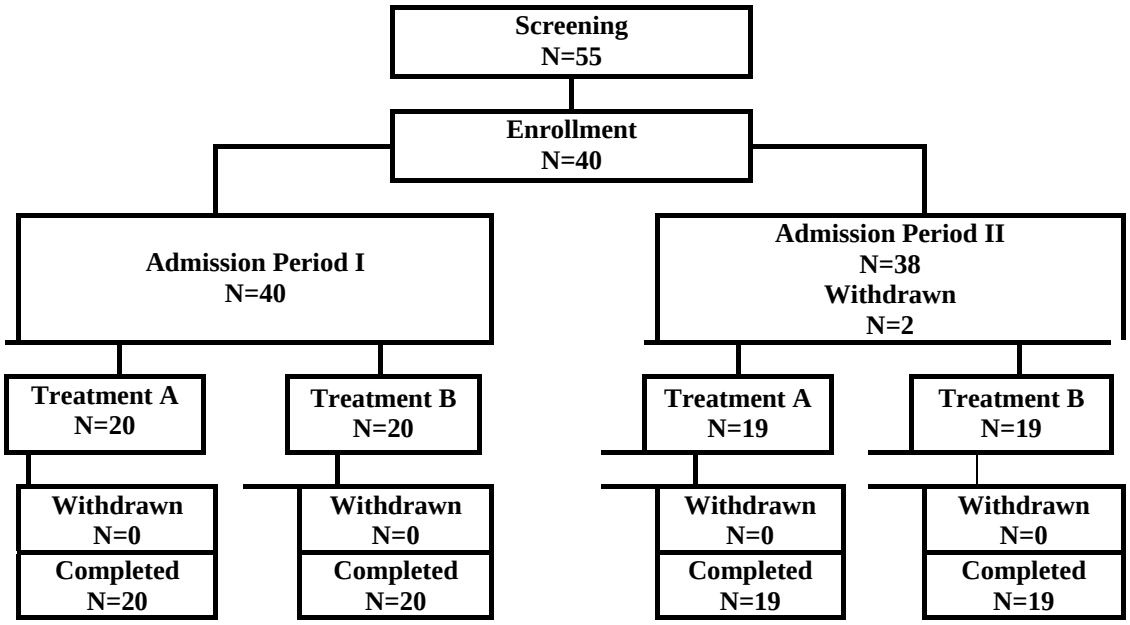
55 healthy subjects were screened according to the selection criteria described in the Study Protocol, while 40 volunteer were admitted to the study. All participating subjects were treated as a single group:

Group	Number of Subjects	Study Day 1 of Study Period I	Number of Subjects	Study Day 1 of Study Period II
1	1-40	23/01/2006	1-40*	06/02/2006

*: Subject No. 29, 40 are withdrawals

Each subject was examined thoroughly during screening procedures as described in the Study Protocol (the screening time being set to be not more than 1 month prior to the first study drug administration of study period I). 40 subjects were enrolled and admitted and completed period I. 38 subjects were admitted to period II and completed the study.

Figure 2 Disposition of Subjects



4.2. Withdrawals and Exclusions

During this study, 55 subjects were screened. Six subjects withdrew for significant variation of their lab result, and nine subjects withdrawn for personal reason and a total of 40 were admitted in period I, 38 subjects were admitted to period II, two subjects withdrew for personal reason before study drug administration of period II, and 38 subjects completed study Period II. For details on withdrawals, see appendix 2.1.

4.3.Demographic Characteristics

The demographic characteristics of the 36 subjects, who completed the study and involved in the pharmacokinetic analysis, were as follows:

- Age ranging between 18 and 39 years (24 ± 4.27 years).
- Weight at screening examination between 60 and 95 kg (74 ± 8.48 kg)
- Height between 160 and 184 cm (173 ± 5.86 cm).

For detailed information about the demographic data obtained for the 38 volunteers at screening examination see appendix 2.3.

4.4. Variations from the Study Protocol

Slight variations from the Study Protocol concerning the clinical laboratory tests were observed (a list of these variations is found in appendix 2.2. "Impact of the Variations from the Study Protocol on the Study Outcome"). These variations were judged by the Principal Investigator to be insignificant.

5. SAFETY EVALUATION

The study was performed according to EMEA GCP guidelines under the direction of the Clinical Investigator. There were no significant deviations from the Study Protocol that could have affected the outcome of this study. All subjects met the inclusion criteria described in the Study Protocol. Foreseeable risks were weighed before study initiation. Rights, safety and well being of the study subject were considered the most important issue, prevailing over interests of science and society. All medical care and medical decisions were given on behalf of the subjects under the full supervision of Principal Investigator. All the subjects were in good health before the initiation of the study. The clinical results of the screened laboratory examinations (biochemistry, hematology, and urine analysis) were, occasionally, outside their respective normal ranges but not to an extent to be considered clinically significant by both the Clinical and the Principal Investigator.

5.1. Benefit to risk ratio

Adverse effects encountered during the study were very minimal. The study outcome will help ensure safe and clinically reliable management of hyper lipidemia, therefore benefiting society by lowering treatment costs. The drug is a prescribed medication; we therefore, conclude that in view of the small risks involved, it was significant to perform this study.

5.2. Extent of Exposure

During this study, 40 subjects volunteered. The study is designed as a single dose two-way crossover. Thus, the risk to a healthy volunteer taking two oral doses of 40 mg atorvastatin from the two products (*Atorvastatin and Lipitor®)*, with a 14-day interval is minimal

5.3. Adverse Events

5.3.1. Brief Summary of Adverse Events

The study's subjects were asked to inform the clinical staff of occurrence of any adverse events (AE) immediately once experienced. Furthermore, the clinical staff was instructed to check on the subjects for the occurrence of any AE at specified time intervals (before dosing, 1.00, 2.00, 3.00, 4.00, 7.00, 9.00 and 12.00 hours from study's drugs administration) and to notify immediately the Clinical Investigator. The Clinical Investigator monitored closely the subjects for AE and took all necessary actions that he saw best in the subject's interest.

5.3.2. Display of Adverse Events

During the study none of the subjects were reported to manifest adverse events.

5.4. Clinical Laboratory Evaluation

Medical histories and the laboratory tests of haematology, hepatic and renal functions were all performed for each subject on screening examination. Only medically healthy subjects with clinically normal laboratory profiles were enrolled in the study. Physical examination was performed after completion of Period II of the study. Values of laboratory results are detailed in appendix 2.7.

5.5.Vital Signs, Physical Assessment and Other Clinical Observations

Each subject received a thorough physical assessment and vital signs evaluation (blood pressure, pulse, respiratory rate and temperature) on screening examination. The subjects received the same physical assessment, as well as, the vital signs evaluation on follow up examination, which was within 24 hours from collecting the last sample in period II.

5.6.Safety and Tolerance

Having completed the study, subjects underwent a thorough physical assessment on follow up examination to assure their safety.

Clinical assessment for all subjects was carried out to evaluate their tolerability to the study's medications. Study subjects demonstrated good tolerance to the two study's drugs. See appendix 2.8. "Clinical Assessment for All Subjects".

6. RESULTS AND BIOEQUIVALENCE EVALUATION

6.1.Data Sets From Study Subjects

Demographic data and all clinical assessment along with laboratory evaluation were performed for all enrolled subjects. However, for pharmacokinetic evaluations the data from the 36 subjects, who were crossed over and completed the balance design, were included in the calculation.

6.2. Adjustment due to anomalies

6.2.1. Adjustment due to collection anomalies

There were collection anomalies reported for which adjustments to the data sets were deemed necessary. For details see appendix 2.2.

6.2.2. Adjustment due to analytical anomalies

Where necessary samples of concentrations above the Upper Limit Of Quantification (ULOQ) of calibration curves were diluted.

6.2.3 Adjustment due to pharmacokinetic anomalies

There were no pharmacokinetic anomalies for which adjustments to the data sets were considered necessary.

6.2.4. Non-zero pre-dose concentrations

There were no instances of non-zero pre-dose concentrations of the drug.

6.3. Handling of withdrawals

There were no samples from withdrawals in the study.

6.4. Pharmacokinetic Parameters

Drug plasma levels were designated as surrogate parameters to indicate clinical activity. Primary pharmacokinetic parameters were set to be C_{max}, $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$ and were also considered to be the bioequivalence determinants. Finally, K_e, t_{max}, $t_{½e}$ and $(AUC_{0\rightarrow t}$ /$AUC_{0\rightarrow\infty})$% were set as the secondary pharmacokinetic parameters

6.5. Statistical inferences

6.5.1. Bioequivalence conclusion

The details of atorvastatin results of this bioequivalence study are shown in Tables 6, 7 and 8 in "Tables and Figures Referred to but not Included in the Text". Bioequivalence could be demonstrated for atorvastatin within the prescribed 90% confidence interval of 80.00-125.00% for $AUC_{0\rightarrow t}$ AUC $_{0\rightarrow\infty}$ and within 75.00 – 133.00 %. for C_{max} with respect to the parametric method on log-transformed data.

The TEST product, *Atorvastatin* tablet (SAJA Pharmaceuticals, Saudi Arabia; 40 mg atorvastatin per tablet), investigated in this study was shown to be bioequivalent with the REFERENCE product; *Lipitor*® tablet (Godecke, Parke Davis Germany; 40 mg atorvastatin per tablet) following an oral dose of 40 mg. Plasma levels may be used as surrogate parameters for clinical activity. Therefore, the data obtained in this study prove, by appropriate statistical methods, the essential similarity of plasma levels of atorvastatin from the TEST product *Atorvastatin* tablet (SAJA Pharmaceuticals, Saudi Arabia) and from the REFERENCE product *Lipitor*® tablet (Godecke, Parke Davis, Germany) suggesting equal clinical efficacy of these two products.

6.5.2. Analysis of Variance (ANOVA)

Analyses of variance (ANOVA) of logarithmically-transformed data for C_{max}, $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$ and for the untransformed data for C_{max}, $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, $t_{½e}$, K_e and t_{max} demonstrated that sequence effect, product effect and period effect for all bioequivalence metrics did not significantly influence the outcome of the study. ANOVA results obtained for each bioequivalence metric are located in "Tables and Figures Referred to but not Included in the Text". Further details may be found in appendix 1.7. "Pharmacokinetics and Statistical Outputs".

7. DISCUSSION AND CONCLUSIONS

This study was a single center, open-label, randomised, single-dose study with two-way crossover design to compare the bioavailability of atorvastatin between two products, in 36 healthy, adult volunteers.

The results of this bioequivalence study showed the equivalence of the two studied products in terms of the rate of absorption as indicated by C_{max} and in terms of the extent of absorption as indicated by $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$. The parametric 90% confidence intervals of the mean values for the TEST/REFERENCE ratio were in each case well within the bioequivalence acceptable boundaries of 80.00-125.00% for $AUC_{0\rightarrow t}$ AUC $_{0\rightarrow\infty}$ and within 75.00 – 133.00 %. for $C_{max.}$

ANOVA analysis on the log-transformed data, C_{max}, $AUC_{0\rightarrow t}$ and $AUC_{0\rightarrow\infty}$ and untransformed data for C_{max}, $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, K_e, $t_{1/2e}$ and t_{max} showed that sequence effect, product or period effect for all these parameters did not significantly influence the outcome of the study. The mean plasma curves of both products are almost superimposable suggesting that not only C_{max} and AUC but also the time course of plasma levels over the whole sampling period are identical.

Since plasma levels are a meaningful surrogate for pharmacodynamic action and adverse events, this demonstrates that an equivalent therapeutic activity and tolerance is to be expected from *Atorvastatin* tablet (SAJA Pharmaceuticals, Saudi Arabia) the TEST product as compared to *Lipitor*® tablet (Godecke, Parke Davis, Germany), the REFERENCE Product.

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