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Bioequivalence study of a new fixed-dose combination tablet containing irbesartan and hydrochlorothiazide in healthy volunteers

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Abstract

Background and objective: The combination antihypertensive therapy has shown greater blood pressure lowering potential as well as better adherence to the treatment. Therefore, a new generic fixed-dose combination containing irbesartan and hydrochlorothiazide was developed and rate and extend of absorption were compared with reference formulation to prove its bioequivalence in healthy volunteers.

Methods: A single-centre, open-label, randomized, two-period, crossover, single dose study under fasting conditions, including at least 7-days washout period, was performed in 30 healthy male and female volunteers. Twenty blood samples were collected in each study period: prior to dosing (0:00) and up to 72:00 hours after dosing and plasma concentrations of irbesartan and hydrochlorothiazide were analysed using preliminary validated methods.

Results: The 90% CIs for the geometric mean ratios of test and reference of Cmax and AUC0–t were 89.22% to 98.80% and 100.58% to 115.11%, respectively, for irbesartan and 91.80% to 122.96% and 94.88% to 117.56%, respectively. Thus, the corresponding ratios of Cmax and AUC0-t for irbesartan and hydrochlorothiazide met the predetermined criteria for bioequivalence (90% confidence intervals of the geometric mean ratios of test and reference within the 80.00% - 125.00%). Both the test and reference products demonstrated good tolerability profile in this population, and no serious AEs were observed.

Conclusions: Therefore, the test product (Irbesartan/hydrochlorothiazide 300/25 mg film-coated tablets, manufactured by Tchaikapharma High Quality Medicines Inc., Bulgaria) and the reference product (CoAprovel 300/25 mg film-coated tablets, manufactured by Sanofi Clir SNC, France) are considered bioequivalent.

Keywords: bioequivalence; irbesartan; hydrochlorothiazide; healthy subjects

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Introduction

Hypertension is a public health problem and leading cause of mortality and disability. Pooling data from population-based studies predicted that the global burden of hypertension would increase by 29% by 2025, reaching close to 1.5 billion **[1, 2].** Data from the NHANES (National Health and Nutrition Examination Survey) with 23,272 participants demonstrated higher mortality rates among hypertensive adults than non-hypertensive adults **[3].**

The high prevalence of hypertension has a substantial impact on the burden of cardiovascular disease worldwide. In a meta-analysis of 61 prospective observational studies each 20 mm Hg higher systolic blood pressure (or 10 mm Hg higher diastolic blood pressure) at ages 40–69 years was associated with more than a twofold difference in the stroke death rate, and with twofold differences in the death rates from ischaemic heart disease (IHD) and from other vascular causes **[4].** Results from a population of 4717 hypertensive men, treated by their physicians according to the standard clinical practice, suggest that after adjustment for age and associated risk factors uncontrolled hypertensive subjects presented an increased risk for cardiovascular disease mortality and for coronary heart disease mortality compared

with controlled subjects **[5].**

Therefore, prompt management of high blood pressure (BP) is important to reduce the risk of target organ damage, for prevention of cardiovascular complications, cerebrovascular events, and death. The primary agents recommended by most guidelines and used as monotherapy and in combination therapy for the treatment of hypertension include thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCBs) **[2].** Evidence from studies using fixed-dose combination (FDC) products has shown greater BP lowering with fixed-dose combination agents as well as better adherence to therapy **[6].**

The combination of ARB and thiazide diuretic results in additive lowering of BP and was recommended for treatment of essential hypertension **[2].** A fixed-dose combination of hydrochlorothiazide and irbesartan showed additive antihypertensive effect in a dose-dependent manner up to hydrochlorothiazide (HCTZ) 25 mg and irbesartan 300 mg with high tolerability in diverse patient groups **[7].** BP-lowering potential and safety profile of irbesartan/HCTZ combination were proved in clinical trials. This combination may also be effective in indications beyond hypertension, including congestive heart failure, post-myocardial infarction management, diabetic nephropathy, and others **[8-10].**

Irbesartan has a high bioavailability (60-80%), a long duration of action, and a small potential for pharmacological interactions due to the nature of the enzymatic pathway involved in its metabolic process. The peak plasma concentration after oral administration of irbesartan occurs at 1.5-2 hours. Irbesartan is eliminated through the liver and kidneys, with 20% of the administered dose detectable in urine; while the rest can be found in the feces; the elimination half-life is 11–15 hours. HCTZ is fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 50 to 80% with peak plasma concentration within 1 h to 2.5 h following an oral dose. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidneys. The pharmacokinetics of irbesartan are not affected by the presence of hydrochlorothiazide and vice versa **[11, 12].**

In the era of high prevalence of hypertension across the world, the development of generic products that meet the criteria of quality and effectiveness for this disease will benefit mainly the patients. The aim the of present paper is to report the results of a bioequivalence study of a newly developed fixed-dose generic product containing 300 mg irbesartan and 25 mg hydrochlorothiazide compared with reference formulation in a single-dose, 2-period, 2-sequence, crossover, and randomized study in healthy volunteers.

Materials and methods

The clinical part of this study was carried out at the Clinic of Clinical Pharmacology and Therapeutics, based at the University Hospital "TsaritsaYoanna-ISUL", Sofia, Bulgaria. The study with all relevant documents was reviewed and approved by the Ethics Committee (EC) of University Hospital "TsaritsaYoanna-ISUL", Sofia, Bulgaria and by the Bulgarian Drug Agency. The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, last revised by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013) **[13]** and that are consistent with the current ICH GCP Guidelines, regulatory requirements of the EMA **[14,15]** and relevant National Laws and Regulations **[16,17].**

Study subjects

Prior to the screening procedure of the study, the volunteers were informed about the nature, purpose, potential risks, anticipated benefits, and discomforts that could arise from their participation; and about their right to withdraw at any time. Subjects documented their willingness to participate by signing an informed consent form.

Eligible volunteers were healthy Caucasian subjects of both sexes (male or female non-pregnant, non-breastfeeding, menopausal, surgically sterile or using adequate contraception method), aged between 18 and 55 years, BMI between 19 and 30 kg/m^2, non-smoking or smoking up to 10 cigarettes a day, able not to smoke from entering the clinical centre until leaving at 24th hour after administration of the investigational product.

All eligible subjects were selected after passing screening examination including collection of demographic data, physical examination, laboratory tests, which included Hematology, biochemistry, urine analysis, HIV and hepatitis B antibody and hepatitis C antigen tests. Medical history of clinically significant current or past diseases, surgical interventions, weight and height measurement, body mass index calculation, vital signs (blood pressure, heart rate, and temperature), ECG (12-lead electrocardiogram) as well as drug abuse tests and breath tests for alcohol were also recorded.

Investigational drug products

The following formulations were used for the study: Irbesartan/Hydrochlorothiazide 300/25 mg film-coated tablets manufactured by Tchaikapharma High Quality Medicines Inc., Bulgaria, as the test product and CoAprovel 300/25 mg film-coated tablets manufactured by Sanofi Clir SNC, France, as the reference product.

Study design and drug administration

The study (EudraCT No: 2017-004862-88) was conducted as a single-center, open-label, randomized, two-period, single-dose, crossover oral bioequivalence study in healthy male and female subjects under fasting conditions. Subjects (n=30) were randomly assigned into 2 groups according to a computer-generated randomization scheme. The volunteers were housed at the clinical facility at least 12 hours prior to dosing in each period. After at least a 10-hours fasting period, one tablet of the test or the reference product was administered to each subject with 240 ml water at room temperature in each period. Following drug administration, study subjects continued in fasting conditions for a minimum of 4 h, and standard meals were served at scheduled times (at 4, 8 and 12 hours post-dose for each period). No fluid intake was allowed from 1 h before until 1 h after drug administration. In the second period, the volunteers received the alternate product (test or reference) after a washout period of at least 7 days.

Blood sampling

Venous blood samples were collected into pre-labeled vacutainers containing K_2EDTA as anti-coagulating agent by a catheter inserted into the forearm at 0:00 (pre-dose) and at 0:15, 0:30, 0:45, 1:00, 1:15, 1:30, 1:45, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 12:00, 24:00, 36:00, 48:00 and 72:00 hours after the dose for the test and the reference drugs.

Following centrifugation (1900 g, 4 ± 4°C, 10 min) the separated plasma was transferred in pre-labeled polypropylene tubes and stored at the clinical center at -20ºC ± 5ºC until transportation to the bio analytical laboratory **(Figure 3).**

Bio analytical Assay

Concentrations of irbesartan and hydrochlorothiazide in plasma samples were analysed by Anapharm Bioanalytics, Barcelona, Spain, using validated methods in compliance with the EMA Guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**) [18]. Quantitative analysis for plasma concentration of irbesartan involved a protein precipitation extraction procedure with methanol. Irbesartan and internal standard (Irbesartan-d_4) were measured by reversed phase high performance liquid chromatography coupled to a tandem mass spectrometry detector (LC/MS/MS). The detection conditions of operated mass spectrometer were positive ion mode with detection by multiple reactive monitoring using the m/z transitions 429.20 to 207.10 for irbesartan and 433.20 to 211.10 for irbesartan-d4, respectively. Quantitation was by peak area ratio method. A weighted ($1/X^2$) linear regression was performed to determine the concentration of the analyte. The linearity of standard curve was confirmed ($r \geq 0.9991$) over the concentration range of 20.01 to 8003.20 ng/ ml with suitable accuracy and precision. Hydrochlorothiazide is extracted from an aliquot of human EDTA plasma using a solid-phase extraction procedure with strong anion-exchange and reversed phase 30 mg plates and then injected into a liquid chromatograph equipped with a tandem mass spectrometry detector. Quantitation was by peak area ratio method. A weighted ($1/X^2$) linear regression was performed to determine the concentration of the analyte. The detection conditions of operated mass spectrometer were negative ion mode with detection by multiple reactive monitoring using the m/z transitions 295.80 to 268.90 for hydrochlorothiazide and 300.70 to 270.70 for hydrochlorothiazide-$^{15}N_2$-^{13}C-D_2, respectively. Calibration curves were found to be consistently accurate and precise over the 1.01 to 302.40 ng/mL calibration range.

Before using these methods to determine the clinical levels, the methods were fully validated for linearity, precision, accuracy, specificity, matrix selectivity, sensitivity, recovery, matrix effect, dilution integrity, carryover, reinjection reproducibility, and stability. The validated stability periods of the samples covered the periods between the blood draws and the completion of the analytical determination. Both studies were conducted in compliance with the Principles of Good Laboratory Practice.

Safety assessments

The initial clinical screening was carried out not more than 30 days before the beginning of the study and included demographic data, brief anamnestic data (medical and medication history), physical examination, determination of body temperature, weight and height, measurements of BP and pulse rate (PR) after 5 minutes resting in a sitting position, standard ECG (12 lead). All of the clinical laboratory tests (albumin, alkaline phosphatase, AST, ALT, GGT, urea, calcium, chloride, glucose, phosphorus, potassium, serum creatinine, sodium, total bilirubin, uric acid, total protein, cholesterol: total cholesterol, HDL, LDL, triglycerides, as well as complete blood count with differential count, hemoglobin, hematocrit) were performed at a contracted and certified laboratory (medical diagnostic laboratory RAMUS). The volunteers were also checked for the presence of HBsAg, HCV-Ab and HIV-Ab in serum. The following parameters were determined in urine: pH, specific gravity, protein, glucose, ketones, bilirubin, urobilinogen, occult blood and cells, nitrite, leukocytes. On admission, the subjects underwent tests for alcohol, drugs, and pregnancy (urine test), while vital signs (blood pressure, heart rate, temperature) were also measured.

All volunteers were under continuous supervision by qualified medical staff throughout their stay in the clinical facility to ensure their safety and wellbeing. During both study periods, the vital signs (blood pressure and heart rate) of each volunteer were periodically measured. Throughout the study, the physicians questioned subjects periodically about symptoms of possible adverse events (AEs), and subjects were encouraged to report any unusual symptoms. All volunteers were subjected to a post-study examination and laboratory tests on the day of the last sampling in the second period or not more than 14 days thereafter. All AEs, independently of their intensity, seriousness, and causality to the investigated drugs, were recorded in source data forms and transferred in case report forms of the volunteers.

Pharmacokinetic parameters and statistical analysis

For the purpose of bioequivalence analysis, the primary pharmacokinetic parameters were AUC_{0-t} (area under the plasma concentration-time curve from zero to the last measurable concentration) calculated by the linear trapezoidal rule and C_{max} (maximum drug concentration in plasma) observed directly from experimental data. Additional evaluated pharmacokinetic parameters were T_{max} (time of maximum concentration), $AUC_{0-\infty}$ (area under the plasma concentration-time curve from zero to infinity), $t_{1/2}$ (terminal half-life time), K_{el} (terminal rate constant of elimination), residual area under the concentration-time curve.

The test product was compared to the reference product with respect to the primary pharmacokinetic parameters using an analysis of variance (ANOVA) with sequence, subject (sequence), product and period effects as fixed effects after logarithmic transformation of the data. Bioequivalence assessment was based on a predefined acceptance criterion of 80–125% for the 90 % confidence interval for the ratio of the test and reference products for the log-transformed data of AUC_{0-t} and C_{max}. The statistical significance was established at $p \leq 0.05$ for all statistical tests. The data listings, descriptive statistics, statistical analysis and graphical presentations were generated with SAS/STAT

package. WinNonLin package was used for pharmacokinetic computations **(Table 3).**

Based on a bioequivalence range from 80.0 to 125.0% for C_{max} and AUC_{0-t}, a within-subject coefficient of variation (CV%) not greater than 20%, and a "test/reference" mean ratio of 93%, 28 subjects were needed to achieve a power of 80% at an alpha level of 0.05 to show bioequivalence. To account for possible drop-outs/withdrawals additional 2 subjects were included in the study, and as a result, thirty (30) subjects were enrolled.

Results

Study population

Thirty (30) volunteers were included (17 males and 13 females) and were randomized into the study. One subject was withdrawn due to an observed adverse event with concomitant medication intake; hence twenty-nine (29) completed the crossover design receiving a single dose of both formulations and were included in the pharmacokinetic analysis **(Figure 1).** The discontinued subject was dosed only with a test product during the first period and was withdrawn before the 72 h blood sample in period 1. Demographic data of the subjects included in the study are presented in **(Table 1).**

Safety

Twelve (12) of the thirty (30) subjects experienced a total of sixteen (16) adverse events (AEs) during the study. The reported adverse events during treatment with test product were mild headache (subjects 005 and 010) and mild dizziness (subject 001), possibly related to the treatment; as well as mildly represented frequent urination (subjects 016 and 026) considered as probably related to the treatment. Moderate to severe toothache unrelated to the administered test drug was reported by one subject twice during period 1 (subject 003).

During treatment with a reference product, were reported mild tachycardia possibly related to the administered drug and mild abdominal pain not related to the study drug. Furthermore, a moderate headache was observed (subjects 013), which was considered possibly related to the study drug and needed a concomitant treatment of paracetamol 500 mg.

Both test and reference products were generally well tolerated after single-dose administration. All AEs were mild or moderate, with no serious AEs or SUSARs (suspected unexpected serious adverse reactions) being observed. Most of the subjects who reported having an AE recovered spontaneously within a few hours or a few days of drug administration.

There was only one withdrawal during the study. Subject 003, who experienced moderate to severe toothache after check out at 24 h of Period 1, was treated with paracetamol 500 mg and lidocaine 50 mg. The adverse event was deemed unrelated to the study medications and it was resolved by tooth extraction. The subject was withdrawn by decision of the principal investigator because of possibility of pharmacokinetic profile altering interaction of the concomitant medication applied and the study drug.

Pharmacokinetic Analysis

The validated bio analytical methods were successfully applied to evaluate the bioequivalence of two tablet formulations of Irbesartan/Hydrochlorothiazide in healthy volunteers: Irbesartan/Hydrochlorothiazide film-coated tablets of Tchaikapharma High Quality Medicines Inc., Bulgaria (test product) were compared with CoAprovel 300/25 mg film-coated tablets manufactured by Sanofi Clir SNC, France (reference product). **(Figure 2)**

Table 2 present the mean values and standard deviations for primary and additional pharmacokinetic parameters and geometric means for C_{max} and AUC_{0-t}. In the case of irbesartan,

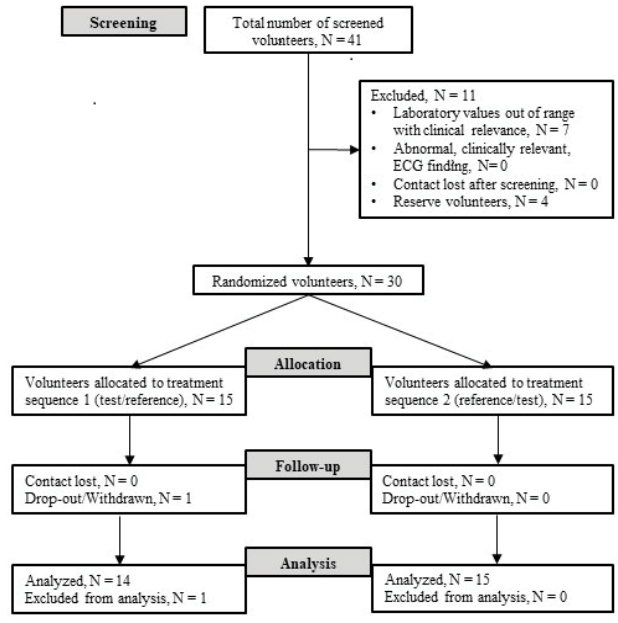


Figure 1 Disposition of the volunteers.

Table 1. Descriptive statistics of demographic data.

n=30	**Age,** years	**Height,** cm	**Weight,** kg	**BMI,** kg/m^2
Mean	39.10	169.63	70.80	24.62
SD	9.87	10.87	10.83	3.05
%CV	25.23	6.41	15.29	12.39
Min	18	149	51.8	19.77
Max	55	198	98	29.91

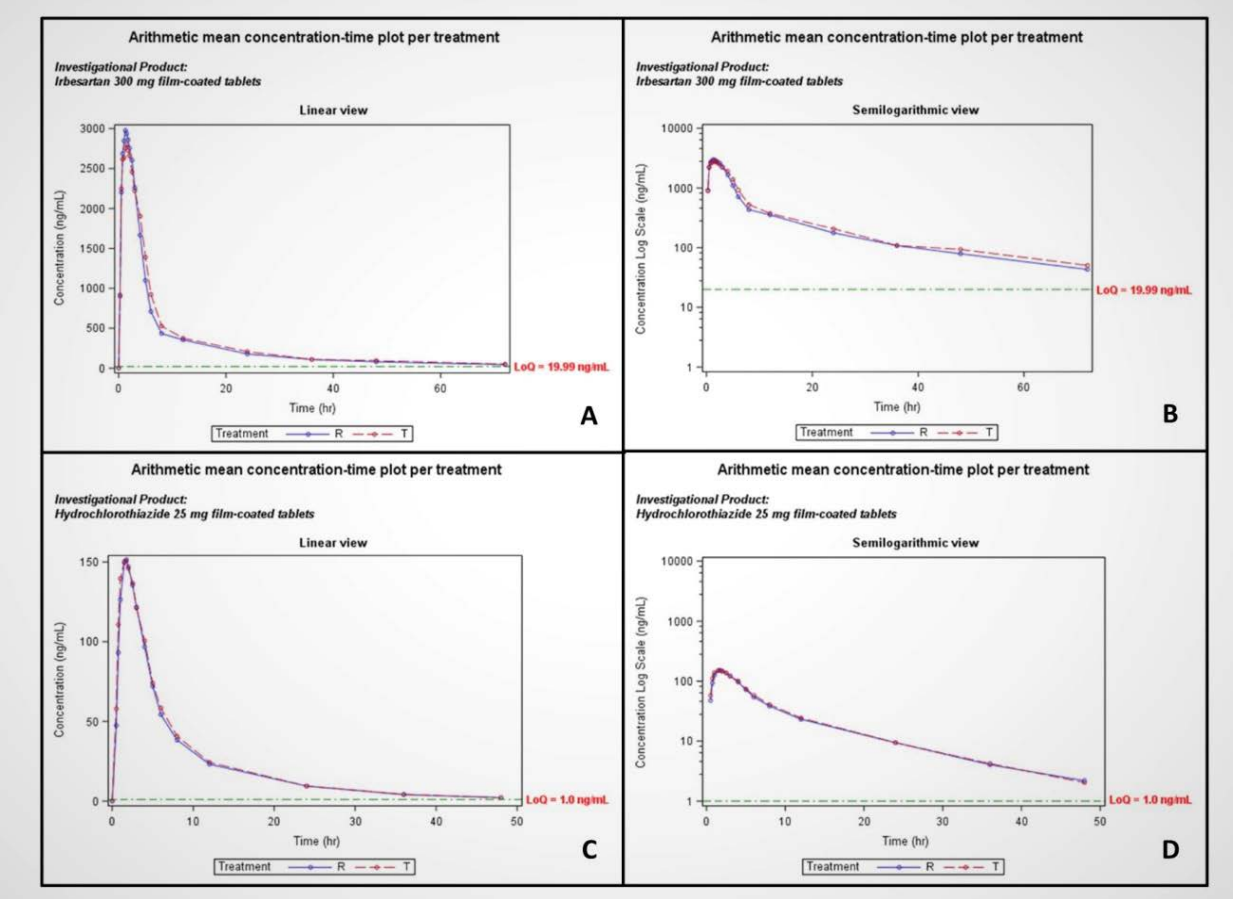


Figure 2 Arithmetic means plasma concentration–time profiles for (A) irbesartan and (C) hydrochlorothiazide; Semi-log scale of the mean plasma concentration-time profiles for (B) irbesartan and (D) hydrochlorothiazide.

the observed average C_{max} and AUC_{0-t} were 3329.96±901.28 ng/mL and 22126.34±7193.63 h.ng/mL for the test product and 3511.12±945.84 ng/mL and 20299.49±7035.14 h.ng/mL for the reference product, respectively. In the case of hydrochlorothiazide, the observed average C_{max} and AUC_{0-t} were 180.94±54.37 ng/mL and 1136.73±244.69 h.ng/mL for the test product and 174.56±60.13 ng/mL and 1092.92±297.53 h.ng/mL for the reference product, respectively. The geometric mean plasma concentration-time curves of irbesartan and hydrochlorothiazide after administration of a single dose from the test or the reference products on fasting conditions in 30 healthy volunteers are shown in figure 2 (A,C). The semi-log scale mean plasma concentration-time profiles of irbesartan and hydrochlorothiazide are shown in figure 2 (B,D) **(Table 2).** Bioequivalence assessment

The point estimates with 90% confidence intervals of the geometric mean ratios of test and reference (T/R) in the study were found to be 93.89% (89.22 - 98.80%) for C_{max} and 107.60% (100.58 - 115.11%) for AUC_{0-t} for irbesartan and 106.24% (91.80 - 122.96%) for C_{max} and 105.62% (94.88 - 117.56%) for AUC_{0-t} for hydrochlorothiazide. Thus, the corresponding ratios of C_{max} and $AUC0_{-t}$ met the predetermined criteria for bioequivalence (90% confidence intervals of the geometric mean ratios of test and reference within the 80.00% - 125.00%) **(Table 3)**.

Discussion

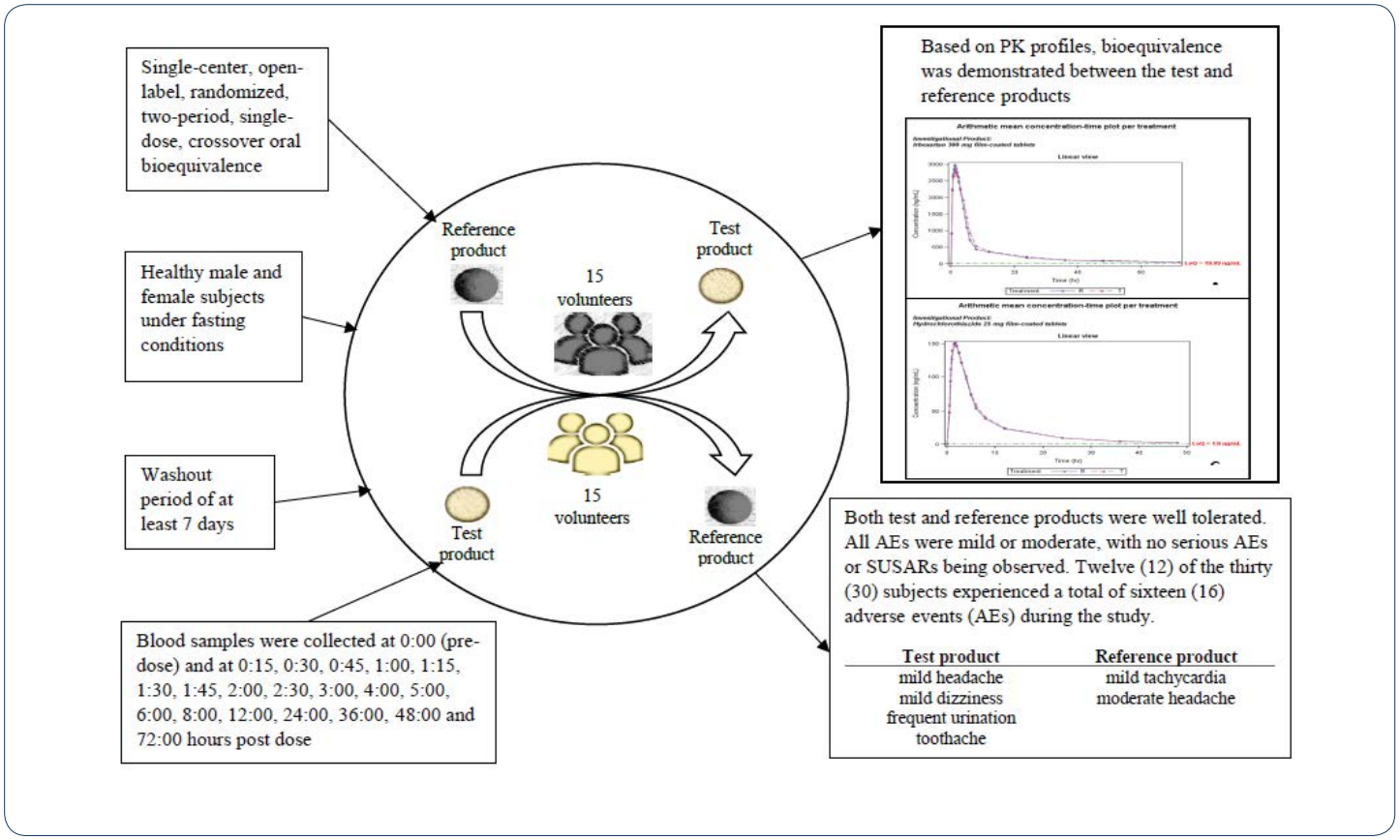
The purpose of bioequivalence testing is to determine whether a new formulation's bioavailability and pharmacokinetic parameters significantly differ from those of a reference formulation. Therefore, the generic formulations with proven bioequivalence and safety profile to branded products could substitute the available reference products without repeating

Table 2. Pharmacokinetic parameters (Mean±SD) of irbesartan (300 mg) and HCTZ (25 mg) of the test and reference products [in brackets are given geometric means].

PK parameter	Irbesartan		HCTZ	
	Test	Reference	Test	Reference
AUC0-t, ng.h/ml	22126.34±7193.63	20299.49±7035.14	1136.73±244.69	1092.92±297.53
	[20934.60]	[19176.53]	[1112.13]	[1047.19]
AUC0-∞, ng.h/ml	23652.31±8425.07	21549.90±7876.58	1167.87±249.84	1124.73±303.84
Res,%	5.72±4.80	5.18±5.18	2.68±1.42	2.95±1.41
C_{max}, ng/ml	3329.96±901.28	3511.12±945.84	180.94±54.37	174.56±60.13
	[3214.56]	[3389.74]	[173.54]	[163.00]
T_{max}, h	1.93±1.36	1.64±0.89	1.79±1.08	1.81±0.75
T1/2	16.77±8.59	14.92±8.12	10.11±1.91	9.97±1.88
lnC_{max}	8.0800±0.2712	8.1300±0.2710	7.0140±0.2126	6.9539±0.3139
lnAUC0-t	9.9500±0.3483	9.8600±0.3444	5.1564±0.2934	5.0938±0.4006

Table 3. Bioequivalence assessment summary for irbesartan (300 mg) and hydrochlorothiazide (25 mg).

	Parameter	T/R Ratio (%)	90% CI (%)	Intrasubject (%)
Irbesartan	AUC_{0-t}	107.6	100.58- 115.11	31.61
-	C_{max}	93.89	89.22- 98.80	25.08
HCTZ	AUC_{0-48}	105.62	94.88- 117.56	12.49
-	C_{max}	106.24	91.80- 122.96	12.98



clinical trials in patients and on the pharmaceutical market will be registered quality and cost-effective generic drugs, analogs to significantly more expensive reference products, after the expiry of their patent protection.

The test product and the reference product had comparable pharmacokinetic characteristics and well-tolerated profiles. The elimination half-life for irbesartan was 16.77 hours and 14.92 hours for reference and test products, respectively, whereas for hydrochlorothiazide it was 10.11 hours and 9.97 hours. The washout period of 7 days was sufficient and no pre-dose concentrations were shown. The study demonstrated that the mean test AUC_{0-t} values of 22126.34 (±7193.63) ng.h/ml and

1136.73 (±244.69) ng.h/ml for irbesartan and hydrochlorothiazide respectively are comparable with the reference product and with results of other studies **[19, 20].** The administration of fixed-dose combination irbesartan/hydrochlorothiazide in fasting condition resulted in maximum plasma concentrations (C_{max}) around 3300 ng/ml for irbesartan and 180 ng/ml for hydrochlorothiazide, which were comparable with reference product; around 3500 ng/ml for irbesartan and 174 ng/ml for HCTZ. These findings are consistent with other studies that assessed the pharmacokinetics of irbesartan and HCTZ as monoproducts **[21, 22]** and as a fixed-dose combination **[19].** The C_{max} values peaked in the test and reference formulations at 1 h 56 min and 1 h 38min, respectively, for irbesartan and 1 h 47 min and 1 h 49 min for hydrochlorothiazide. All AEs were mild or moderate and spontaneously recovered, and there were no serious AEs. Hence, both the test and reference products were well tolerated.

In the present study, the average AUC_{0-t} for all volunteers (except one, dosed with test formulation) was a good representative of the extent of absorption since the average AUC_{0-72} obtained was found to be greater than 80% of the average AUC_{0-inf}. The results suggest that 90% confidence intervals of the geometric mean ratios of test and reference were completely within the predefined bioequivalence criteria of 80.00% to 125.00% for the primary pharmacokinetic parameters of AUC_{0-t} and C_{max}.

Conclusions

The present study found that the test product (Irbesartan/hydrochlorothiazide 300/25 mg film-coated tablets, manufactured by Tchaikapharma High Quality Medicines Inc., Bulgaria) and the reference product (CoAprovel 300/25 mg film-coated tablets, manufactured by Sanofi Clir SNC, France) were considered bioequivalent. Both the test and reference products demonstrated a good tolerability profile in this population, and no serious AEs were observed.

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