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Oral Bioequivalence Study of Dapagliflozin 10 Mg and Rosuvastatin 20 Mg Tablet in Healthy Indian Subjects Under Fasting Conditions

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ABSTRACT

The objective to conduct this study is to compare the rate and extent of absorption and also to monitor the safety and tolerability of a single dose of Dapagliflozin 10 mg and Rosuvastatin 20 mg Tablets using Open label, balanced, randomized single-dose, two-treatment, two-sequence, two-period two-way Crossover design in 24 Healthy, Adult, Human Subjects Under Fasting Conditions. All subjects were dosed with the one tablet of Test product (T): Dapagliflozin 10 mg and Rosuvastatin 20 mg Tablet or reference product (R): Forxiga® 10 mg (Dapagliflozin 10 mg Tablets) and Rosulip 20 (Rosuvastatin 20 mg Tablets orally while in sitting position with 240 mL of 20% aqueous glucose solution as per the randomization schedule at ambient temperature. The LC-MS/MS method was developed at Bion Clinicals Pvt. Ltd., Pune, India to determine Plasma concentrations of Dapagliflozin and Rosuvastatin.

The result showed ratios of geometric least squares means of the test product (T) and reference product (R) for the Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Dapagliflozin were found to be 93.21%, 97.09% and 96.12% respectively and for Rosuvastatin were found to be 101.29%, 100.91% and 99.39%.

The 90% confidence intervals for the ratios of geometric least squares means for the Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Dapagliflozin were found to be 84.38% - 102.97%, 93.45% -100.88% and 92.60%-99.78% respectively.

The 90% confidence intervals for the ratios of geometric least squares means for the Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Rosuvastatin were found to be 91.53%-112.09%, 91.39%-111.43% and 88.16%-112.04% respectively.

In conclusion, the 90% confidence intervals of the differences of least squares means for the Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Dapagliflozin and Rosuvastatin were within the bioequivalence acceptance limits of 80.00 - 125.00% and thus the test product (T): Dapagliflozin 10 mg and Rosuvastatin 20 mg Tablet and reference product (R): Forxiga® 10 mg (Dapagliflozin 10 mg Tablets) and Rosulip 20 (Rosuvastatin 20 mg Tablets) were found bioequivalent

with respect to rate and extent of absorption. The Dapagliflozin 10 mg and Rosuvastatin 20 mg oral dose was well tolerated and was found safe.

Keywords: Pharmacokinetic, Pharmacodynamic, Dapagliflozin, Rosuvastatin

Introduction

Diabetes mellitus is a heterogeneous group of disorders characterized by hyperglycemia due to an absolute or relative deficit in insulin production or action. The chronic hyperglycemia of diabetes mellitus is associated with end organ damage, dysfunction, and failure, including the retina, kidney, nervous system, heart, and blood vessels. The treatment of diabetes mellitus is determined by the etiopathology and is most commonly subdivided in type 1 and type 2 diabetes mellitus. There is a greater propensity towards hyperglycemia in individuals with coexisting genetic predisposition or concomitant drug therapy such as corticosteroids. The etiological classification of diabetes and related disorders of glycemia includes, (1) type 1; (2) type 2; (3) those due to specific mechanisms and diseases; and (4) gestational diabetes mellitus.

Type 2 diabetes mellitus (T2DM) is an expanding global health problem, closely linked to the epidemic of obesity. Individuals with T2DM are at high risk for both microvascular complications (including retinopathy, nephropathy and neuropathy) and macrovascular complications (such as cardiovascular comorbidities), owing to hyperglycaemia and individual components of the insulin resistance (metabolic) syndrome. The multiple pathogenetic disturbances present in T2DM dictate that multiple antidiabetic agents, used in combination, will be required to maintain normoglycaemia. The treatment must not only be effective and safe but also improve the quality of life. Several novel medications are in development, but the greatest need is for agents that enhance insulin sensitivity, halt the progressive pancreatic β-cell failure that is characteristic of T2DM and prevent or reverse the microvascular complications [(3)].

Sodium-glucose co-transporter 2 (SGLT2) is predominantly expressed in the S1 segment of the proximal tubule of the kidney and is the major transporter responsible for mediating renal glucose reabsorption. Dapagliflozin is an orally active, highly selective SGLT2 inhibitor that improves glycemic control in patients with type 2 diabetes mellitus (T2DM) by reducing renal glucose reabsorption leading to urinary glucose excretion (glucuresis). Orally administered Dapagliflozin is rapidly absorbed generally achieving peak plasma concentrations within 2 h. Dose-proportional systemic exposure to Dapagliflozin has been observed over a wide dose range (0.1-500 mg) with an oral bioavailability of 78%. Dapagliflozin has extensive extravascular distribution (mean volume of distribution of 118 L). Dapagliflozin metabolism occurs predominantly in the liver and kidneys by Uridine Diphosphate-Glucuronosyltransferase-1A9 to the major metabolite Dapagliflozin 3-O-glucuronide (this metabolite is not an SGLT2 inhibitor at clinically relevant exposures). Dapagliflozin is not appreciably cleared by renal excretion (<2 % of dose is recovered in urine as parent). Dapagliflozin 3-O-glucuronide elimination occurs mainly via renal excretion, with 61 % of a dapagliflozin dose being recovered as this metabolite in urine. The half-life for orally administered dapagliflozin 10 mg was 12.9 h. Maximal increases in urinary glucose excretion were seen at doses ≥20 mg/day in patients with T2DM. No clinically relevant differences were observed in dapagliflozin exposure with respect to age, race, sex, body weight, food, or presence of T2DM. No clinically relevant drug interactions were observed that would necessitate dose adjustment of Dapagliflozin when administered with other antidiabetic or

cardiovascular medications, as well as drugs that could potentially influence Dapagliflozin metabolism [4].

Rosuvastatin is a new HMG-CoA reductase inhibitor with unique pharmacological and pharmacokinetic properties. It has additional HMG-CoA reductase enzyme-binding interactions that cause tighter binding, has substantial active transport into hepatocytes, and has the lowest IC50 for sterol synthesis in hepatocytes. Rosuvastatin 10 mg and 80 mg dosages have superior low-density lipoprotein (LDL) cholesterol-lowering efficacy as compared to atorvastatin 10 mg and 80 mg. Rosuvastatin 10 mg has also been shown to have superior LDL reductions to 20 mg of both simvastatin and pravastatin. This agent can raise high-density lipoprotein (HDL) 8% to 12% and lower triglycerides by 10% to 35%. Rosuvastatin is a hydrophilic agent with poor penetration in extrahepatic tissue such as human umbilical vein endothelial cells and fibroblasts. It also has a low potential for cytochrome P450 drug interactions and can be dosed in the morning or night. In conclusion, Rosuvastatin is an agent with molecular alterations that provide it with unique pharmacologic and pharmacokinetic effects. As such, it is a novel and unique HMG-CoA reductase inhibitor for the treatment of hyperlipidaemia [(5)].

The objective of this study was to investigate the pharmacokinetics and bioavailability of two different oral Dapagliflozin and Rosuvastatin formulations following single dosing in healthy adult subjects in order to prove the bioequivalence between both preparations. According to the CPMP, Note for Guidance on the Investigation of Bioavailability and Bioequivalence [10], two medicinal products are bioequivalent if their bioavailabilities (rate and extent) after administration of the same molar dose are similar to such degree that their effects with respect to both efficacy and safety will be essentially the same. This requirement is fulfilled, if the 90% confidence intervals of the AUC ratio and Cmax ratio are within a predefined acceptance range (80%–125%) [10].

Materials and Methods

Study Drugs: Test Product: Dapagliflozin 10 mg and Rosuvastatin 20 mg Tablets were supplied and manufactured by Exemed Pharmaceuticals (Vapi, Gujarat, 396195, India) for oral administration. Reference Products: Forxiga® 10 mg (Dapagliflozin 10 mg Tablets) were Imported and Marketed by AstraZeneca Pharma India Ltd. 12th Mile Bellary Road, Bangalore-560063, India and Rosulip 20 (Rosuvastatin 20 mg Tablets) Manufactured by: Cipla Ltd., (Unit II) Taza Block, Rorathang, Sikkim-737133, India. The study drugs were stored at 22±2°C and a relative humidity of 60±5%.

Study Designs: The study was an open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period two-way crossover at a single site in India (Bion Clinicals Pvt. Ltd., Pune). The study investigated the safety, tolerability, and PK of Dapagliflozin and Rosuvastatin after oral dosing in fasting, healthy adults.

The single-dose oral bioequivalence study has been divided into two periods: In period 01, twelve (12) subjects were given a single dose (one tablet) of test drug Dapagliflozin 10 mg and Rosuvastatin 20 mg Tablets of Exemed Pharmaceuticals in Gujarat, India, and twelve (12) subjects were given a single dose of reference drug, one tablet of Forxiga® 10 mg (Dapagliflozin 10 mg Tablets) of AstraZeneca Pharma India Ltd., and one tablet of Rosulip 20 (Rosuvastatin 20 mg Tablets) of Cipla Ltd. The subjects fasted for 04 hours following the administration of the study drug.

In a period 02, Following a 09-day washout period, the subjects received the alternate formulation to that they were given in period 01 (12 received the test product and 12 received the reference product) under identical conditions.

The subjects fasted overnight for at least 10.00 hours prior to drug administration. All safety and tolerability data and available PK data at the TPD dose were reviewed by the clinical investigator.

Ethical Considerations

The Pulse Multi Speciality Hospital's Ethics Committee approved the study on April 08, 2023. Written informed consent was given by all participants. The study was carried out in accordance with the EC approved protocol and clinical research guidelines established by the basic principles defined in the ICH-GCP guidelines, the ICMR Ethical Guidelines for Biomedical Research on Human Subjects (2017), the Declaration of Helsinki (Fortaleza, Brazil, October 2013), G.S.R. 227(E) New Drugs and Clinical Trials Rules, 2019, and Guidelines for Bioavailability and Bioequivalence Studies, Central Drugs Standard Control Organization, March 2005.

Study Populations: For this study, subjects who were aged between 18 -45 years with a body mass index (BMI) between 18.50-30.00 kg/m^2 (inclusive of both) and body weight not less than 50.00 kg and agreeing to use appropriate contraceptive measures were had been selected. All enrolled subjects were in good health based on medical history, clinical examination, along with vital signs, recording of electrocardiogram and laboratory test results, tested negative for drugs of abuse and for pregnancy (applicable for female subject), and were competent to provide written informed consent.

Randomization

Subjects were assigned to either of the treatments using computer generated randomization schedules.

Study Procedures: Subjects were checked-in for period 01 and for period 02 and the total duration of the study was 14 days from the day of check-in of the first period till the end of the second period. Extra subjects E1 and E2 were enrolled for the study on the day of period 01 check-in. Subject E1 and E2 checked-out from the facility after dosing of the required number of subjects.

The study was conducted in two periods, after overnight fasting of at least 10.00 hours, A single dose of either test product (T) or reference product (R) was administered orally to the subjects in sitting posture with approximately 240 mL of 20% aqueous glucose solution at ambient temperature in period 01, whereas in period 02, Following a washout period of 09 days, a single dose of the alternate product to that of used in period 01 was dosed to each subject.

Serial blood samples (01 pre-dose (0.00 hour) sample and 28 post-dose samples in each period (up to 72.00 hours) were taken during each study period.

Blood samples were collected through an indwelling cannula placed in a forearm vein using a disposable syringe or alternatively through venipuncture with disposable syringes and needles in the case of cannula blockage. An intravenous indwelling cannula was kept *in situ* as long as possible during the 24.00 hours post-dose in-house stay in each period. Normal saline solution was injected to keep the cannula patent, and blood samples were drawn after discarding the first 0.5 mL of normal saline mixed blood from the cannula (except ambulatory samples). Ambulatory samples were collected by fresh venipuncture. Four (04) mL of blood was collected in pre-labelled (Study No., Subject No., Period No., Time Point) polypropylene tubes (initially stored at -70 ± 10°C) containing K_2EDTA anticoagulant at each sampling time point.

Blood samples were collected at the following time points during treatment periods in studies.

0.00 hour (pre dose) and at 0.25, 0.50, 0.75, 1.00, 1.25. 1.50, 1.75, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 8.00, 9.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours

post-dose. The blood samples at 36.00, 48.00 and 72.00-hours post-dose samples were collected on ambulatory basis (i.e., on separate visit).

After collection of blood samples from all subjects at a particular time point, the centrifugation under refrigeration was commenced within 01 hour of last blood sample collection.

The subjects received a standard meal on the day of check-in and at approximately 4.00, 8.00- and 12.00-hours post-dose in each period. During housing, the meal menu was identical in terms of content and quantity for all periods. Drinking water was not allowed from one hour before until one hour after dosing in each period (except for 20% aqueous glucose solution, given during dosing).

Safety Assessment: Subjects who had received at least one dose of the investigational product were included in the safety evaluation. Safety assessment was based on clinical laboratory evaluation, ECG recordings, clinical examination, along with vital signs (axillary temperature, radial pulse rate, sitting blood pressure and respiratory rate) measurement and post-study clinical laboratory safety evaluation. Laboratory assessments (haematology, biochemistry, serology and urine analysis) and ECG recordings were done at the time of screening. Clinical examination along with vital signs (axillary temperature, radial pulse rate, sitting blood pressure, respiratory rate) and questioning for well-being were undertaken at the time of screening, during check-in and before check-out of each period. Vital signs (axillary temperature, radial pulse rate and sitting blood pressure) and questioning for well-being were recorded within 2.00 hours prior to dosing in each period. Vital signs (sitting blood pressure, radial pulse rate and axillary temperature) and questioning for well-being were measured and recorded at 1.00, 4.00 and 8.00 hours after dosing (within ± 45 minutes of the scheduled time) and when subject reported for ambulatory samples. Blood glucose level was monitored using a handheld glucometer at 2.00, 5.00, 10.00 and 24.00 hours (within ± 30 minutes of the scheduled time) after dosing. A urine screen for drugs of abuse (amphetamines, barbiturates, benzodiazepines, marijuana, cocaine and morphine) and a breath test for alcohol consumption were done during check-in of each period. Subjects were questioned for well-being at the time of clinical examination and recording of vital signs. Clinical examination, measurement of vital signs and questioning for well-being was performed prior to check-out only for the subjects who were dosed.

A safety sample was collected for post-study safety assessment (haematology and biochemistry) from all dosed subjects at the end of the study.

Pharmacokinetics: PK analysis was performed to characterize the pharmacokinetic profile of the test product in comparison to the reference product. Plasma concentrations of Dapagliflozin and Rosuvastatin were determined using a LC-MS/MS method developed at Bion Clinicals Pvt. Ltd., Pune, India.

Intra-subject variability of the pharmacokinetic parameters $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$ of Dapagliflozin and Rosuvastatin was estimated using the root mean square error obtained after carrying out an analysis of variance for bioequivalence assessment. Also, the relative bioavailability was evaluated by calculating least squares mean ratios for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for Dapagliflozin and Rosuvastatin (test) to Dapagliflozin and Rosuvastatin (reference). The 90% confidence intervals for the ratios of least squares means between drug formulations were calculated for the Ln-transformed data of both $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$ of Dapagliflozin and Rosuvastatin. Additionally, the power of the test to detect a 20% difference between the test product (T) and reference product (R) was computed and reported for Dapagliflozin and Rosuvastatin.

BIOANALYTICAL PROCEDURES

Dapagliflozin and Rosuvastatin in plasma was analysed using a LC-MS/MS (Model-AB Sciex 4500) method. All analytical procedures carried out under yellow monochromatic light. Analysis included samples from all dosed subjects (except in period-01 if any subject experiences emesis/ withdrawn/ dropped out after dosing and no post dose samples were collected, then pre-dose sample of such subject would not be analysed. The criteria for repeat analysis as defined in the respective in-house SOP will be followed. The study conducted to establish the validity including accuracy, precision, reproducibility, specificity, recovery and stabilities of the analytical method.

Observations and Results

1. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS :

The mean of age, height, weight and BMI of the subjects who received the dose in the study were 29.0 ±7.15years, 167.5±4.98 cms, 65.04±9.442 Kgs and 23.11±2.607 Kg/m^2 respectively. All subjects were of Asian origin, non-smokers and non-alcohol. Out of the 24 subjects, 22 were non-vegetarians, while 2 were vegetarian.

2. PHARMACOKINETIC AND STATISTICAL EVALUATION :

Table 1: Descriptive Statistics of Pharmacokinetic Parameters of Test Product (T) for Dapagliflozin (N = 23)

Parameter	Treatment	N	Mean	Std Dev	Minimum	Median	Maximum	Std Error	%CV	Geometric Mean
$AUC_{\%\_Extrap\_obs}$	T	23	2.454	1.148	1.139	2.287	5.242	0.239	46.789	2.228
$AUC_{0-\infty}$	T	23	809.393	156.451	505.930	773.721	1117.903	32.622	19.329	794.836
AUC_{0-t}	T	23	789.953	154.845	487.540	753.058	1092.334	32.287	19.602	775.276
C_{max}	T	23	138.921	46.531	75.979	135.257	257.300	9.702	33.494	132.199
K_{el}	T	23	0.099	0.025	0.048	0.097	0.158	0.005	25.560	0.096
$t_{1/2}$	T	23	7.468	2.165	4.377	7.142	14.475	0.452	28.997	7.209
T_{max}	T	23	1.712	0.901	0.750	1.500	4.500	0.188	52.647	1.530

Table 2: Descriptive Statistics of Pharmacokinetic Parameters of Reference Product (R) for Dapagliflozin (N = 23)

Parameter	Treatment	N	Mean	Std Dev	Minimum	Median	Maximum	Std Error	%CV	Geometric Mean
$AUC_{\%\_Extrap\_o}$	R	2	3.446	2.113	1.301	2.647	9.095	0.441	61.31	2.995

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$AUC_{0-\infty}$	R	23	841.073	146.839	495.539	852.715	1082.329	30.618	17.459	827.731
AUC_{0-t}	R	23	813.177	149.689	479.104	810.346	1064.360	31.212	18.408	799.017
C_{max}	R	23	146.309	34.335	100.150	134.933	238.223	7.159	23.468	143.057
K_{el}	R	23	0.087	0.029	0.051	0.076	0.156	0.006	33.210	0.083
$t_{1/2}$	R	23	8.767	2.640	4.448	9.165	13.570	0.551	30.116	8.373
T_{max}	R	23	1.678	0.907	0.750	1.500	4.500	0.189	54.030	1.498

Table 3: Geometric Least Squares Means, Ratios, 90% Confidence Intervals, ISCV and Power for Pharmacokinetic Parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of Dapagliflozin (N=23)

Parameter	GLSMT	GLSMR	T/R Ratio	90% CI Lower	90% CI Upper	Power	BE
C_{max}	132.8235	142.4972	93.21%	84.38%	102.97%	97.8%	YES
AUC_{0-t}	777.1068	800.3625	97.09%	93.45%	100.88%	100.0%	YES
$AUC_{0-\infty}$	796.6430	828.7721	96.12%	92.60%	99.78%	100.0%	YES

Table 4: Descriptive Statistics of Pharmacokinetic Parameters of Test Product (T) for Rosuvastatin (N = 23)

Parameter	Treatment	N	Mean	Std Dev	Minimum	Median	Maximum	Std Error	%CV	Geometric Mean
$AUC_{\%\_Extrap\_obs}$	T	23	7.067	9.003	2.168	5.811	47.463	1.877	127.401	5.363
$AUC_{0-\infty}$	T	23	214.233	68.198	128.006	192.747	365.820	14.220	31.833	204.381
AUC_{0-t}	T	23	198.391	66.291	120.568	177.721	356.376	13.823	33.414	188.750
C_{max}	T	23	15.741	6.164	10.649	12.945	30.058	1.285	39.160	14.836
K_{el}	T	23	0.073	0.023	0.009	0.074	0.108	0.005	31.251	0.067
$t_{1/2}$	T	23	12.571	14.058	6.390	9.365	76.052	2.931	111.834	10.283
T_{max}	T	23	4.555	1.857	0.750	4.500	9.000	0.387	40.767	4.044

Table 5: Descriptive Statistics of Pharmacokinetic Parameters of Reference Product (R) for Rosuvastatin (N = 23)

Parameter	Treatment	N	Mean	Std Dev	Minimum	Median	Maximum	Std Error	%CV	Geometric Mean
$AUC_{\%\_Extrap\_obs}$	R	23	8.573	9.867	2.941	6.783	51.999	2.057	115.095	6.657
$AUC_{0-\infty}$	R	23	219.545	81.025	118.629	202.099	387.586	16.895	36.906	205.923
AUC_{0-t}	R	23	198.992	74.189	109.345	185.098	353.222	15.470	37.283	186.766
C_{max}	R	23	15.367	5.343	10.379	13.668	30.410	1.114	34.767	14.663
K_{el}	R	23	0.067	0.024	0.008	0.069	0.105	0.005	35.286	0.060
$t_{1/2}$	R	23	14.413	16.380	6.580	10.105	86.611	3.415	113.646	11.473
T_{max}	R	23	4.803	2.200	0.500	4.500	9.000	0.459	45.812	4.055

Table 6: Geometric Least Squares Means, Ratios, 90% Confidence Intervals, ISCV and Power for Pharmacokinetic Parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of Rosuvastatin (N=23)

Parameter	GLSMT	GLSMR	T/R Ratio	90% CI Lower	90% CI Upper	Power	BE
C_{max}	14.7975	14.6087	101.29%	91.53%	112.09%	97.4%	YES
AUC_{0-t}	187.9013	186.2027	100.91%	91.39%	111.43%	97.8%	YES
$AUC_{0-\infty}$	203.7529	205.0137	99.39%	88.16%	112.04%	92.3%	YES

Dapagliflozin: The ratios of geometric least squares mean of the test product (T) and reference product (R) for the Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Dapagliflozin were found to be 93.21%, 97.09% and 96.12% respectively.

The 90% confidence intervals for the ratios of geometric least squares means for the Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Dapagliflozin were found to be 84.38% -102.97%, 93.45% -100.88% and 92.60%-99.78% respectively.

Rosuvastatin: The ratios of geometric least squares mean of the test product (T) and reference product (R) for the Ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ of Rosuvastatin were found to be 101.29%, 100.91% and 99.39% respectively.

The 90% confidence intervals for the ratios of geometric least squares means for the Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Rosuvastatin were found to be 91.53%-112.09%, 91.39%-111.43% and 88.16%-112.04%respectively.

3. PHARMACOKINETIC DATA:

Figure 1 : Linear Plot of Mean Plasma Concentrations of Dapagliflozin vs. Actual Time for Test Product (T) and Reference Product (R) (N = 23)

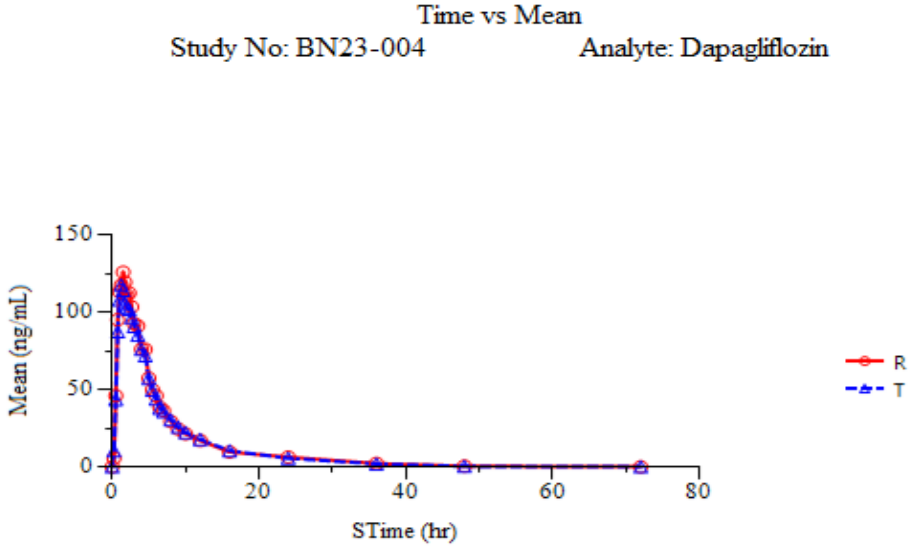


Figure 2 : Ln Linear Plot of Mean Plasma Concentrations of Dapagliflozin vs. Time for Test Product (T) and Reference Product (R) (N = 23)

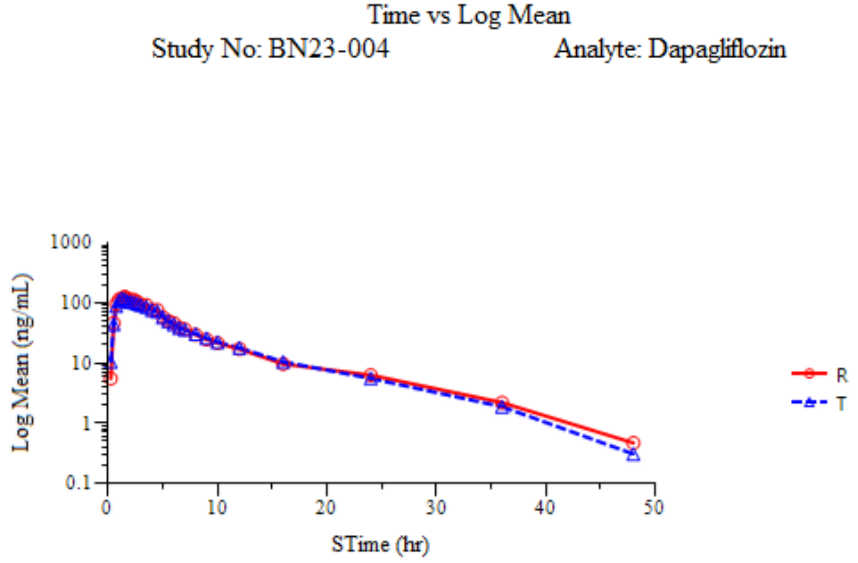


Figure 3 : Linear Plot of Mean Plasma Concentrations of Rosuvastatin vs. Actual Time for Test Product (T) and Reference Product (R) (N = 23)

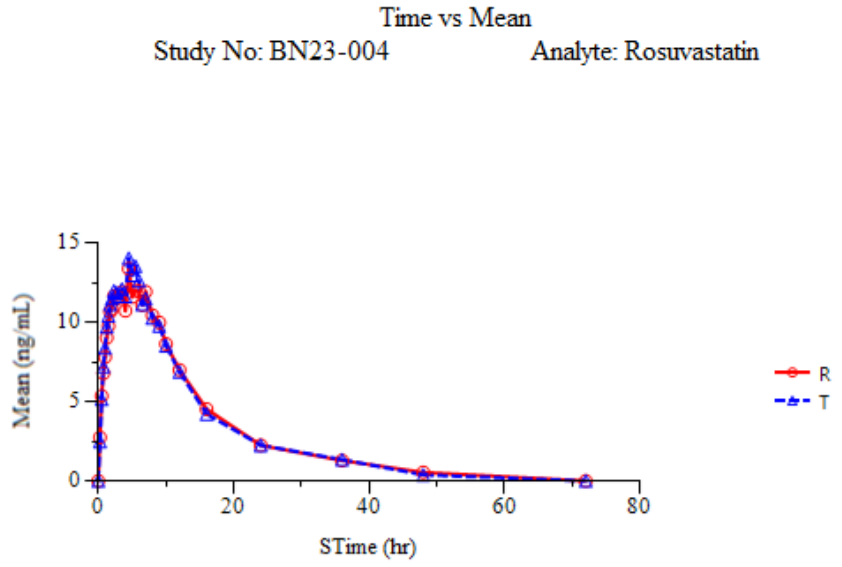
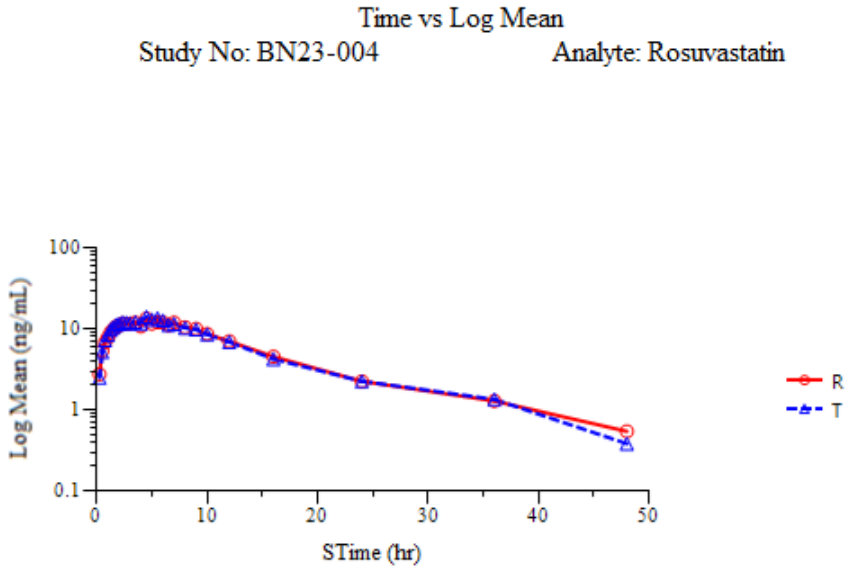


Figure 4 : Ln Linear Plot of Mean Plasma Concentrations of Rosuvastatin vs. Time for Test Product (T) and Reference Product (R) (N = 23)



4. SAFETY

The test and reference products were comparable in their safety and tolerability in healthy, adult, human male subjects under fasting conditions.

5. ADVERSE EVENTS

No mild, moderate, severe, serious or life-threatening adverse events were reported during the course of the study.

DISCUSSION

Bioequivalence studies are performed to determine the in vivo biological equivalence between two different proprietary pharmaceutical preparations in the pharmaceutical industry. Their rationale is to provide a resemblance between a generic medicine and its corresponding innovator medicine in terms of safety, quality, efficacy, dosage form, strength, and route of administration. This study was performed in 24 healthy volunteers with single dose of Dapagliflozin 10 mg and Rosuvastatin 20 mg Tablet in a crossover manner.

This study compared the bioequivalence of single dose Dapagliflozin 10 mg and Rosuvastatin 20 mg Tablet, a test and reference product. This study found that 90% CI for AUC_{0-t} and $AUC_{0-\infty}$ were within the bioequivalence acceptable range of 80% to 125%. Moreover, the C_{max} profile of Dapagliflozin 10 mg and Rosuvastatin 20 mg was almost identical for test and reference products. The study found that Geometric Least Squares Means of C_{max} for test drug was 132.8235 and that of reference drug was 142.4972 which showed T/R ratio of 93.21% (90%CI 84.38%-102.97%) and ISCV of 19.8% suggesting that the test drug was bioequivalent.

The Geometric Least Squares Means of AUC_{0-t} and $AUC_{0-\infty}$ for the test drug were 777.1068 and 796.6430, respectively, while for the reference drug, they were 800.3625 and 828.7721. Both ratios, 97.09% for AUC_{0-t} and 96.12% for $AUC_{0-\infty,}$ along with narrow confidence intervals (90%CI), indicated bioequivalence with low variability (ISCV) for the test drug.

The test product was well tolerated by all the volunteers under fasting conditions. No adverse events either mild or moderate were reported and all 24 subjects completed the study.

Dapagliflozin and Rosuvastatin was very well tolerated in the present study with clinically non-significant changes in AST and ALT parameters noted in only 4 subjects. Dapagliflozin and rosuvastatin was generally well tolerated in all participants even in higher dose [7].

Conclusion

The current study completely satisfied the bioequivalence criteria for all three $AUC_{0-\infty,}$ AUC_{0-t}, and C_{max}. All other pharmacokinetic parameters were well comparable between the test and reference preparations, i.e. no relevant differences were found for T_{max} and $t_{1/2}$. Therefore, it can be concluded that the test and reference preparations are bioequivalent in the rate and extent of absorption and thus can be used interchangeably in medical practice. The results of this study with healthy Indian volunteers might serve as a reference for future controlled studies of Dapagliflozin and Rosuvastatin in the Indian population.

Bibliography

1. Alam, U.; Asghar, O.; Azmi, S.; Malik, R.A. General aspects of diabetes mellitus. *Handb. Clin. Neurol.* 2014, *126*, 211–222.
2. Kuzuya, T.; Nakagawa, S.; Satoh, J.; Kanazawa, Y.; Iwamoto, Y.; Kobayashi, M.; Nanjo, K.; Sasaki, A.; Seino, Y.; Ito, C.; et al. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. *Diabetes Res. Clin. Pract.* 2002, *55*, 65–85.
3. DeFronzo, R.A.; Ferrannini, E.; Groop, L.; Henry, R.R.; Herman, W.H.; Holst, J.J.; Hu, F.B.; Kahn, C.R.; Raz, I.; Shulman, G.I. Type 2 diabetes mellitus. *Nat. Rev. Dis. Prim.* 2015, *1*, 15019.
4. Kasichayanula, S.; Liu, X.; LaCreta, F.; Griffen, S.C.; Boulton, D.W. Clinical Pharmacokinetics and Pharmacodynamics of Dapagliflozin, a Selective Inhibitor of Sodium-Glucose Co-transporter Type 2. *Clin. Pharmacokinet.* 2014, *53*, 17–27.

5. White, C.M. A review of the pharmacologic and pharmacokinetic aspects of rosuvastatin. *J. Clin. Pharmacol.* **2002**, *42*, 963–970.
6. Trabelsi, F.; Bartunek, A.; Vlavonou, R.; Navratilova, L.; Dube, C.; Tanguay Mm Hauser, T. Single-dose, 2-way crossover, bioequivalence study of two rosuvastatin formulations in normal healthy subjects under fasting conditions. *Int. J. Clin. Pharmacol. Ther.* 2012, *50*, 741–750.
7. Diletti E, Hauschke D, Steinijans VW (1991) Sample size determination for bioequivalence assessment by means of confidence intervals. Int J Clin Pharmacol Ther Toxicol 29: 1-8
8. European Medicines Agency (2010) CPMP/EWP/QWP/1401/98 REV. 1/ CORR**-Guideline on the investigation of bioequivalence. London 1-27.
9. Schuirmann DJ (1987) A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J Pharmacokinet Biopharm 15: 657-680.
10. Note for Guidance on the Investigation of Bioavailability and Bioequivalence Committee for Proprietary Medicinal Products. CPMP/EWP/QWP/1401/ 98. London; 26 July 2001