

The MeViDa Study: Bioequivalence Study of FDC of Dapagliflozin, Vildagliptin SR and Metformin SR in Healthy Indian Volunteers: A Randomized, Open-Label, Crossover Study

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Abstract

Objective: To assess the pharmacokinetics and bioequivalence of Dapagliflozin 10mg + Vildagliptin Sustained Release (SR) 100mg + Metformin SR 1000mg fixed dose combination (FDC) tablets with DAPAMAC V 10 (Dapagliflozin 10mg + Vildagliptin SR 100mg tablets) and Glycomet 1g (Metformin SR 1000 mg tablets) in healthy adult male subjects under fasting conditions.

Material and Methods: This was an open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover, oral bioequivalence study. Volunteers were randomized to receive either a test product or a reference product under the fasting condition with a seven-day washout period. The pharmacokinetics parameters evaluated were maximum plasma concentration (C_{max}), the area under the curve (AUC) at time t (AUC_{0-t}), and the total area under the curve ($AUC_{0-\infty}$). Adverse events were also assessed as safety endpoints.

Results: Twenty-four healthy adult male subjects were randomized, and 24 completed the study. The mean values for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ were almost identical for test and reference products. The 90% confidence intervals of the ratios of adjusted geometric means for the pharmacokinetic parameters, i.e. C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ of the test product, were within the predefined bioequivalence limits of 80.00 to 125.00%. No adverse events or serious adverse events or deaths were reported during the study. All treatments were well tolerated.

Conclusion: The test formulation, Dapagliflozin 10mg + Vildagliptin SR 100mg + Metformin SR 1000mg FDC, were bioequivalent to DAPAMAC V 10 (Dapagliflozin 10mg + Vildagliptin SR 100mg tablets) and Glycomet 1g (Metformin 1000mg SR tablets) in healthy adult male subjects under fasting conditions.

Keywords: Bioequivalence, Fixed-Dose Combination, Dapagliflozin, Metformin, Sustained Release, Vildagliptin, AUC, C_{max}

INTRODUCTION

Globally, type 2 diabetes mellitus (T2DM) is among the leading causes of disability and mortality and is associated with many complications. According to the IMPROVE study involving more than fifty thousand patients in eight countries, there was a high prevalence of complications: nearly 50% suffered microvascular complications, and 28% suffered macrovascular complications. Hence, sustained glycemic control is required to reduce the likelihood of such complications.¹

Pivotal trials like UKPDS, ACCORD, ADVANCE, and VADT have demonstrated that intensive glycemic control reduces the risk of microvascular complications and, when implemented early, significantly reduces cardiovascular disease and mortality. The international consensus also supports the use of combination therapy for patients with glycated hemoglobin (Hb A1c) levels significantly above target.²

It has been suggested that starting combination therapy early in the disease may help preserve β -cell function and slow the decline in glycemic control.³ Besides this, combination treatments exert additive, synergistic, or complementary glucose-lowering effects by addressing several underlying

pathophysiologic components of the disease. Previously, combination medications were administered stepwise as separate tablets. However, fixed-dose combination (FDC) tablets are now becoming increasingly common.⁴ The FDCs combine two or more active drugs in a single dosage form.⁵ An advantage of FDC treatment over individual pills may be better adherence, which has been linked to better glycemic control and reduced drug waste.⁴

Currently, a triple-drug combination, FDC, that includes Dapagliflozin, Vildagliptin sustained release (SR), and Metformin SR, is marketed in India. Dapagliflozin, an SGLT-2 inhibitor, increases glucosuria by an insulin-independent mechanism. It is generally well tolerated, with a low risk of hypoglycemia. It also reduces body weight and blood pressure.⁶

In addition, Dapagliflozin landmark trials such as DECLARE TIMI-58, DAPA-HF, and DAPA-CKD have demonstrated cardioprotective and renoprotective properties and potentially mitigating the risk of death from all causes in individuals with heart failure or impaired renal function.⁷

Vildagliptin, a DPP-4 inhibitor, increases the synthesis of glucagon-like peptide-1 (GLP1) and intensifies its action by

enhancing glucose-dependent insulin production and reducing glucagon release. Furthermore, Vildagliptin is weight-neutral, has a low risk of hypoglycemia, and does not increase the risk of adverse cardiovascular effects.⁸

Thus, Dapagliflozin and Vildagliptin have a mechanism of action complementary to Metformin, with minimal risk of hypoglycemia, weight gain, and cardio and renoprotective benefits. Also, compared to conventional immediate-release formulations, FDCs containing Metformin SR provide equal efficacy with a lower dose frequency and maybe fewer gastrointestinal problems for individuals on Metformin.⁹ Hence, the FDC of Dapagliflozin, Vildagliptin sustained release and Metformin SR seems an appealing, safe, and effective option for T2DM patients who are not achieving glycemic targets or who need intensive glycemic control.

This study was conducted to investigate the pharmacokinetic characteristics, bioequivalence, and safety of the test formulations, Dapagliflozin 10 mg + Vildagliptin SR 100mg + Metformin SR 100mg FDC tablet, and the reference formulation in healthy volunteers in fasting states.

MATERIALS AND METHODS

Study design

This study was an open-label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose bioequivalence study of Dapagliflozin, Vildagliptin SR, and Metformin FDC in healthy, adult, human male subjects under fasting conditions. The study was conducted over 11 days, and a washout of 7 days was maintained between two consecutive dosing periods. The Institutional Ethics Committee approved this clinical study protocol. Written informed consent was obtained from all healthy volunteers before their enrollment in the study.

Study objective

The study's primary objective was to compare the absorption rate and extent and characterize the test product's pharmacokinetic profile with the reference product in normal, healthy, adult male subjects under fasting conditions and assess the bioequivalence. The secondary objective was to monitor the adverse events and ensure the subjects' safety after administering a single dose of the test formulation.

Study population

Healthy male subjects [18–45 years old and a body mass index (BMI) of 18.5–30 kg/m²] with no clinically significant abnormalities in their medical history, who can comply with the study procedures, study specific restrictions and prohibitions and voluntarily give written informed consent were eligible to participate in the study.

The exclusion criteria were: volunteers with systolic blood pressure <90 mm Hg or >140 mm Hg and diastolic blood pressure <60 mm Hg or >90 mm Hg, oral temperature <96.2°F or >99.8°F, pulse rate below 60/min or above 100/min, respiratory rate below 12 or above 20 breaths/min, history of hypersensitivity or an idiosyncratic reaction to investigational drug products or any other related drugs, a known history of cardiovascular, pulmonary, hepatic, renal, gastrointestinal, endocrine, immunological, dermatological, neurological, and musculoskeletal, the habit of alcoholism (>21units of alcohol in a week), and smoking(>9 cigarettes /day). Furthermore, subjects who had used any drugs or substances known to be potent inhibitors or inducers of Cytochrome P450 enzymes within 14 days before investigational product administration were excluded. Moreover, confirmed positive in hepatitis screening (HBsAg/HCV) or for HIV antibody and difficulty in swallowing tablets were the additional exclusion criteria.

Study drug

After overnight fasting of 10.00 hours, a single dose of Dapagliflozin 10mg + Vildagliptin SR 100mg + Metformin 1000mg SR FDC tablets Manufactured by Exemed Pharmaceuticals, Gujarat, India, with DAPAMAC V 10 (Dapagliflozin 10mg + Vildagliptin SR 100mg) Marketed by Macleods Pharmaceuticals Ltd, India and GLYCOMET 1g (Metformin 1000mg SR tablets) Marketed by USV Private Limited, Himachal Pradesh, India was administered with 240±2 mL of 20% aqueous glucose solution followed by 60 mL of the glucose solution administered every 15 minutes (window period of ± 5 minutes) for up to 4 hours after dosing at ambient temperature under fasting condition.

Blood sample collection and processing

All blood samples were collected in prelabeled vacutainers containing K2EDTA as an anticoagulant. Blood samples (5ml each) were drawn at pre-dose ((-2.00 to 00.00 hr) and 0.333, 00.667, 01.00, 01.50, 02.00, 02.50, 03.00, 03.50, 04.00, 04.50, 05.00, 05.50, 06.00, 07.00, 08.00, 12.00, 16.00, 20.00, 24.00, 30.00, 36.00- and 48.00-hours post-dose in each period and collected via an indwelling catheter (when possible) or via direct venipuncture.

The pre-dose sample was collected within 2 hours prior to dosing, and the post-dose samples were collected within ±2 min of the scheduled time for in-house samples; however, the actual time of sample collection was considered for pharmacokinetic and statistical analysis.

The plasma was separated by centrifuging the samples at 3500 rpm at 2-5°C for 10 minutes. The plasma was transferred into pre-labelled tubes in duplicates (approximately 1 mL to aliquot 1 and the remaining to aliquot 2). Within 1 hour of separation, the plasma samples were shifted to ULTF for storage at -70 ± 10°C and stored until subjected to analysis.

Bioanalytical analysis

The plasma concentrations of Dapagliflozin, Vildagliptin and Metformin were analyzed using a validated LC-MS/MS method. The analytical method was developed and validated over a concentration range of 2.797 to 279.514 ng/ml for Dapagliflozin, 2.593 to 259.168 ng/ml for Vildagliptin and 25.826 to 2581.346 ng/mL for Metformin.

Safety evaluation

Safety measurements of blood pressure, pulse rate, and body temperature were performed as specified in the study protocol. Subjects' well-being questionnaires were also performed at all the scheduled vitals recording times. Monitoring for adverse events was conducted while recording subject well-being and throughout the entire study duration.

Pharmacokinetics and Statistical analysis

The primary pharmacokinetic parameters were maximum plasma concentration (C_{max}), the area under the curve (AUC) at time t (AUC_{0-t}), and the total area under the curve (AUC_{0-∞}). The secondary parameters were time to reach C_{max} (T_{max}), elimination of Dapagliflozin's half-life time (t_{1/2}), (AUC% Extrap_{obs}), and elimination rate constant (K_{el}).

Statistical comparison of the PK parameters was conducted using the analysis of variance (ANOVA) using the SAS® statistical software, version 9.4 of SAS (SAS® Institute Inc. USA) for average bioequivalence to assess the bioequivalence between the test and reference product. The model included sequence, treatment, period and subject as fixed effects.

ANOVA was performed in transformed PK parameters, including C_{max} , AUC_{0-t}, and AUC_{0-∞}. The 90% confidence intervals for the ratio of test (T) and reference (R) product

averages (least squares means) derived from the analysis of log (natural) transformed PK parameters must be between 80.00% and 125.00% for bioequivalence.

RESULTS

Subject disposition and demographics

A total of 24 healthy, adult human male subjects were enrolled in the study. The 12 subjects received one of the treatment

products [either test or reference product] in period I, and 12 received one of the treatment products [either test or reference product] in period II as per the randomization schedule. All 24 completed both periods of the study (Figure 1). The mean [\pm standard deviation (SD)] age and BMI were 33.21 (\pm 6.62) years and 25.94 (\pm 2.83) kg/m², respectively. The demographic details of the subjects are shown in Table 1.

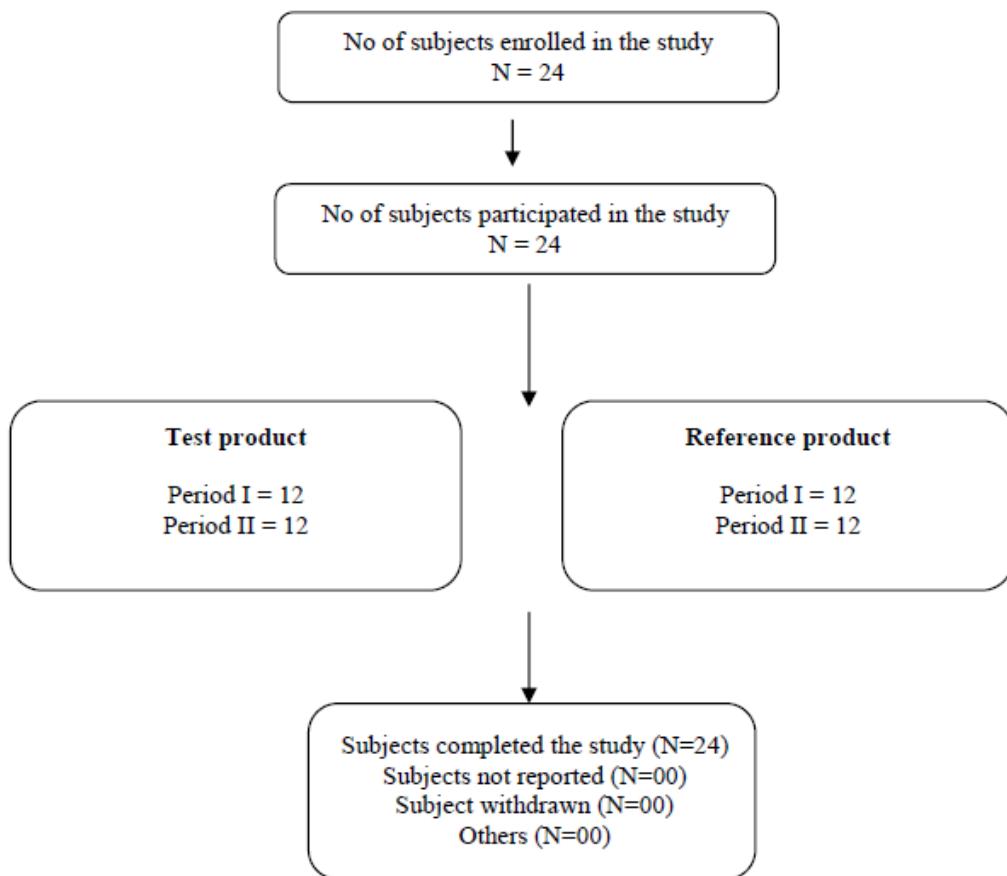


Figure 1: Disposition of subject in the study

Table 1: Demographic details of subjects who participated and completed the study (N=24)

Parameter	Mean \pm SD	CV%
Age (years)	33.21 \pm 6.62	19.93
Height (M)	1.68 \pm 0.05	3.13
Weight (Kg)	73.17 \pm 8.65	11.82
BMI (Kg/m ²)	25.94 \pm 2.83	10.91

BMI: Body mass index; CV: Coefficient of Variation; SD: Standard deviation

Pharmacokinetic results

Dapagliflozin in test product (T) versus reference product (R)

The C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ of Dapagliflozin (10 mg, single-dose) were comparable for test and reference products after administration to healthy human volunteers under fasting conditions (Table 2). The 90% confidence interval (CI) for

C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ of Dapagliflozin were within the bioequivalence limits of 80.00 to 125.00%.

The median value obtained for T_{max} was comparable between the Dapagliflozin test product (1.5 hours) and the reference product (2 hours). Regarding the mean $t_{1/2}$, the mean value obtained for the test product was 6.3 hours, whereas, for the reference product, it was 6.5 hours.

Table 2: Log-transformed analysis of the pharmacokinetic parameters of Dapagliflozin in test product (T) versus reference product (R)						
Pharmacokinetic Parameter	Geometric Least Square Mean		ISCV (%)	T/R Ratio (%)	Power (%)	90% Confidence Interval
	Test Product (T)	Reference Product (R)				
Cmax (ng/mL)	87.74	92.54	23.28	94.81	89.61	84.61 to 106.25
AUC0-t (ng.hr/mL)	502.93	508.33	13.11	98.94	99.92	92.74 to 105.55
AUC0-∞ (ng.hr/mL)	537.35	546.73	13.08	98.29	99.92	92.14 to 104.84

AUC: Area under the curve; Cmax: Maximum plasma concentration; ISCV: Intra-subject variability

Vildagliptin in test product (T) versus reference product (R)

In the fasted state, the pharmacokinetic profile of Vildagliptin SR was similar between the test and reference products (Table 3). The estimation values of geometric mean ratios and 90% CI for both Cmax and AUCs were within the range of bioequivalence, i.e. 80.00–125.00%

The Vildagliptin SR test product and the reference product had comparable median values for Tmax (5.91 vs 5.25 hours). Regarding mean t1/2, the test product's mean value was 4.13 hours, while the reference product's mean value was 4.54 hours.

Table 3: Log-transformed analysis of the pharmacokinetic parameters of Vildagliptin SR in test product (T) versus reference product (R)						
Pharmacokinetic Parameter	Geometric Least Square Mean		ISCV (%)	T/R Ratio (%)	Power (%)	90% Confidence Interval
	Test Product (T)	Reference Product (R)				
Cmax (ng/mL)	174.75	174.10	31.86	100.38	69.29	86.04% TO 117.1
AUC0-t (ng.hr/mL)	1798.67	1887.51	20.70	95.29	94.50	86.09% TO 105.48
AUC0-∞ (ng.hr/mL)	1896.56	1952.24	19.53	97.15	96.22	88.27% TO 106.92

AUC: Area under the curve; Cmax: Maximum plasma concentration; ISCV: Intra-subject variability

Metformin in Test product (T) versus Reference product (R)

The mean values for Cmax, AUC0-t and AUC0-∞ were almost identical for the Metformin SR test and reference product (Table 4). The 90% CIs of the main pharmacokinetic parameters were

within the equivalent interval (80.00–125.00%), and the test and reference formulations were bioequivalent under single-dose administration in fasting conditions. The median Tmax was 5.25 vs 5 hours for test vs reference products. The mean t1/2 was 4.24 hours for the test product vs. 4.17 hours for the reference product.

Table 4: Log-transformed analysis of the pharmacokinetic parameters of Metformin SR in test product (T) versus reference product (R)						
Pharmacokinetic Parameter	Geometric Least Square Mean		ISCV (%)	T/R Ratio (%)	Power (%)	90% Confidence Interval
	Test Product (T)	Reference Product (R)				
Cmax (ng/mL)	1401.81	1463.07	22.50	95.81	91.24	85.82% TO 106.97
AUC0-t (ng.hr/mL)	15316.31	14539.15	27.25	105.35	80.36	92.26% TO 120.29
AUC0-∞ (ng.hr/mL)	15599.77	14858.03	26.89	104.99	81.23	92.1% TO 119.69

AUC: Area under the curve; Cmax: Maximum plasma concentration; ISCV: Intra-subject variability

Safety evaluation

No adverse events, serious adverse events, or deaths were reported in the study. There were no clinically abnormal changes in vital signs. The investigational products (test and reference) were safe and well tolerated.

DISCUSSION

Though lifestyle interventions are a cornerstone in T2DM management, most patients need pharmacological therapy to achieve adequate glycemic control. The progressive decline in β -cell function warrants the use of dual or triple-drug combination therapy.¹⁰ The development of FDC, a combination of two or more drugs formulated in a single dosage form, helps improve compliance and offers additive benefits of two or more active drugs. FDCs are useful in the management of various conditions chronic conditions.¹¹

The evidence suggests poor treatment adherence in T2DM patients, which frequently falls short of the recommended cutoff point of 80%. The complex nature of T2DM therapy drug regimens and pill burden could be a contributing factor to low adherence.¹² FDC therapy could simplify individual treatment regimens for T2DM and reduce non-adherence risk. As a result, this strategy may help more patients follow their treatment plans and accomplish their glycemic targets, reducing the long-term risk of T2DM complications.¹²

A bioequivalence study of FDC must be conducted to get regulatory approval for marketing. In India, a bioequivalence study of FDC is required when one of the active ingredients is approved for < 4 years, irrespective of FDC approval outside India.¹¹ The rate and extent of absorption of each component of the FDC must be the same as those of each component of the approved FDC in the country.¹³

The findings of the present study demonstrated that the test formulation, Dapagliflozin 10mg + Vildagliptin SR 100mg + Metformin SR 1000mg FDC tablets, was bioequivalent to DAPAMAC V 10 (Dapagliflozin 10mg + Vildagliptin SR 100 mg) and GLYCOMET 1g (Metformin SR 1000mg tablets) in normal healthy adult human male subjects under fasting condition. The adjusted geometric mean ratios of FDCs to their respective reference formulation and two-sided 90% CIs for AUC and Cmax were all within the predefined acceptance range of 80.00–125.00%. The FDC of Dapagliflozin 10mg + Vildagliptin SR 100mg + Metformin SR 1000mg was well tolerated. No severe or serious adverse events were reported.

The FDC of Dapagliflozin 10 mg + Vildagliptin SR 100 mg + Metformin SR 1000 mg may offer a therapeutic alternative for T2DM patients, including those requiring treatment intensification. This FDC may be suitable for a wide range of patients, including those with established cardiovascular disease or indicators of high risk, established heart failure or chronic kidney disease. Moreover, the FDC of Dapagliflozin 10 mg + Vildagliptin SR 100 mg + Metformin SR 1000 mg can reduce the pill burden and may improve disease management among patients with more complex medication demands who have demonstrated poor medication adherence.

The present study's limitation is that it did not compare the pharmacokinetic data of the test and reference product under fed conditions; therefore, the effect of food on drug pharmacokinetics was not evaluated.

CONCLUSION

The FDC of Dapagliflozin 10mg + Vildagliptin SR 100mg + Metformin 1000mg SR tablet is bioequivalent to the

corresponding reference formulation in healthy adult male subjects under fasting conditions. The FDC was well tolerated, and no apparent safety or tolerability issues were observed.

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