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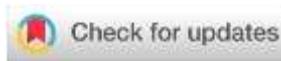
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Research Article

Pharmacokinetic and Pharmacodynamics Study of Multiple Oral Doses of Vildagliptin Sustained Release 100 Mg Tablets under the Fed State in Healthy Volunteers

Chetan Doshi¹, SB Sridhar², Ashish Birla³, Ashish Prasad⁴, Pramod Kadam⁵, Sona Warrier^{6*}¹Chief Scientific Officer, Research and Development, USV Private Limited, Mumbai, India²Head, Clinical Research, USV Private Limited, Mumbai, India³Vice President, Scientific Services, USV Private Limited, Mumbai, India⁴Asst General Manager, Scientific Services, USV Private Limited, Mumbai, India⁵Manager, Clinical Research, USV Private Limited, Mumbai, India⁶Deputy Manager, USV Private Limited, Mumbai, India

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*Address for Correspondence:

Dr Sona Warrier, Deputy Manager, USV Private Limited, Mumbai, India

Abstract

Background: Type 2 diabetes mellitus (T2DM) and its associated complications and comorbidities often require polypharmacotherapy, resulting in a high pill burden and reduced therapy adherence, thereby increasing the risk of adverse outcomes. Given this, we evaluated the pharmacokinetic and pharmacodynamic profile of the vildagliptin 100 mg sustained release (SR) administered once daily compared to vildagliptin 50 mg immediate release (IR) administered twice daily in healthy, adult human subjects under fed conditions.

Material and methods: This was a randomized, balanced, open-label, two-treatment, two-period, two-sequence, crossover multiple oral dose study in healthy adult subjects under fed conditions. The subjects were randomized to receive either a test product, i.e., vildagliptin SR 100 mg once daily, or a reference product, i.e., vildagliptin 50 mg twice daily. The duration of the study was 25 days. The primary pharmacokinetic parameter evaluated was the area under the concentration-time curve for one dosing interval at steady-state (AUC_{0- τ , ss}). Bioequivalence was determined by assessing whether the 90% confidence intervals (CIs) for the geometric mean ratio of test to reference drug fell within predefined margins of 80% –125% for AUC_{0- τ , ss}. The pharmacodynamics parameters evaluated were percent dipeptidyl-peptidase-4 (DPP-4) inhibition and weighted average percent DPP-4 inhibition. The safety assessment was based on clinical laboratory evaluation, chest, ECG recordings, clinical examination, blood glucose monitoring, and post-study clinical laboratory safety evaluation.}

Results: Forty healthy adult males completed the study. There was no significant difference between the pharmacokinetic and pharmacodynamic profiles in reference and test products. The mean \pm standard deviation (SD) values of AUC_{0- τ , ss} for test and reference product was 2689.06 \pm 835.47 2875.57 \pm 703.85 ng. hr/mL, respectively. The 90% CIs of geometric least-square means of test/reference ratio for AUC_{0- τ , ss} with vildagliptin SR 100 mg tablet was 86.32-97.26% within the bioequivalence acceptance range. The test and reference product showed over 90% inhibition of DPP-4 activity with multiple doses. The weighted average percent of DPP-4 inhibition (0-24 hrs) was 92.66% with the test product and 93.26% with the reference product. Both products were well tolerated during the entire study period. No serious adverse events (AEs) were reported during the study.

Conclusion: The two formulations of vildagliptin, i.e., vildagliptin SR 100 mg once daily and vildagliptin 50 mg twice daily, demonstrated similar pharmacokinetic and pharmacodynamic profiles under fed conditions in healthy adult males. Both formulations were bioequivalent and well tolerated.

Keywords: Bioequivalence, DPP-4, Immediate release, Pharmacodynamics, Pharmacokinetics, Sustained release, T2DM, Vildagliptin.

INTRODUCTION

Since 2006, gliptins or dipeptidyl-peptidase-4 (DPP-4) inhibitors have been available to treat type 2 diabetes mellitus (T2DM).¹ There has been a rapid increase in interest in DPP-4 inhibitors as they complement and extend traditionally available therapeutic options for treating T2DM.² DPP-4 inhibitors inhibit the inactivation of the "incretin" hormones, namely glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, leading to increased glucose-

dependent insulin secretion, slowed gastric emptying, and reduced postprandial glucagon and food intake.³ It is estimated that DPP-4 inhibitors have the potential to lower HbA1c by 0.5 to 1.0%, and their safety profile is favorable.⁴

Currently, in this class, eleven medications are available. They differ in their binding processes despite having a similar mode of action, affecting their therapeutic and pharmacological profiles. Vildagliptin is a reliable and well-tolerated DPP-4 inhibitor. Studies in India demonstrate its effectiveness and

safety across various age groups in the presence of comorbidities and diabetic complications.⁵ Conventionally, vildagliptin is available as an immediate release (IR) 50 mg tablet administered twice daily.⁶ Due to the need to treat complications as well as the existence of comorbidities, T2DM is a significant contributor to polypharmacy.⁷ According to several studies, individuals with comorbidity and those taking several or twice-daily regimens exhibit lower adherence than those on monotherapies and once-daily regimens.⁸ Thus, vildagliptin 100 mg once daily sustained release formulation (SR) was developed to address the patient's treatment adherence needs. The SR formulation disperses 100 mg of the medication for a more extended period at a set pace using a polymer matrix structure that promotes the controlled release.⁵

This study was conducted to characterize the pharmacokinetic and pharmacodynamic profile of the vildagliptin SR 100 mg tablet once daily and vildagliptin 50 mg administered twice daily in healthy, adult human subjects under fed conditions.

METHODS AND MATERIALS

Subjects

Eligible healthy subjects were male and nonpregnant females 18 – 45 years of age with body mass index (BMI) of 18.5-30.0 kg / m² and body mass not less than 50 kg. The study included all subjects considered healthy based on vital signs, physical examinations, clinical laboratory tests, and normal or clinically insignificant ECG recording and chest X-ray (P/A view). The eligible subjects must have negative urine tests for drugs of abuse or illicit drug substances and alcohol. The women of childbearing potential must have a negative β -HCG pregnancy test within 21 days before the study's initiation and a negative urine pregnancy test before check-in of each period. They must be using an acceptable form of contraception.

The main exclusion criteria were: Known hypersensitivity to vildagliptin or any component, history, or presence of diabetes, significant cardiovascular, pulmonary, hepatic, renal gastrointestinal, endocrine, immunological, dermatological, neurological, or psychiatric disease or disorder, cancer, smoking or alcohol abuse, history of easy bruising or bleeding, positive screening test result for HIV, Hepatitis B, Hepatitis C, and VDRL, participation in another clinical trial within 90 days, pregnant or nursing females, and use of prescription or nonprescription drugs (including herbal remedies) within two weeks. Subjects who consumed caffeine and /or xanthine-containing foods or beverages and grapefruit and/ or its juice and poppy-containing foods for at least 48 hours before check-in of each period and throughout their stay in the facility were excluded from the study.

Study design

This was a randomized, balanced, open-label, two-treatment, two-period, two-sequence, crossover multiple oral dose study in healthy, adult human subjects under fed conditions. Randomization was done using the PROC PLAN procedure of SAS® (SAS Institute Inc., USA) version 9.4. We used vildagliptin SR tablet 100 mg (Batch no. 0320320; manufactured by USV Private Ltd) as a test product and Galvus® (vildagliptin) 50mg tablet (Lot no. BEV45, manufactured by Novartis Europharm Limited) as a reference product.

Duration of study

The total duration of the study was 25 days from the day of check-in of the first period till the end of the second period. Subjects were confined in the clinical facility to ensure an

overnight fast of at least 10 hours before administration of the investigational product on Day 1. Subjects remained in the facility up to 24 hours after morning dose administration on Day 7 in each period.

Treatment administration

The test and reference product were administered after overnight fasting of at least 10 hours for day 1 and 8 hours for day 2 to day 6 and fasting of at least 2 hours prior to the night dose of the reference product. From day 1 to day 6, meals or snacks were provided during check-in and at approximately 4, 8, and 14 hours after morning dosing in each period. On day 7, meals or snacks were provided during check-in, 30 mins before dosing (high-fat, high-calorie breakfast), and at approximately 4, 8, and 11.50 hours (high-fat, high-calorie dinner) after each period. Test and reference product tablets were swallowed with 240 mL of 20% aqueous glucose solution at room temperature. Following a washout period of 8 days, a single dose of the alternate product to that used in period one was administered to each subject.

Objective

The objective of the study was to characterize and compare the steady-state pharmacokinetic profile and pharmacodynamics of vildagliptin SR tablet 100 mg vs. vildagliptin 50 mg tablet in normal, healthy, adult human subjects under fed conditions. Also, to monitor the safety and tolerability of test and reference products.

Blood sampling

Blood samples were collected in vacuum tubes containing EDTA-K₂. Pre-dose samples (0 hours) were taken within 5 minutes prior to each morning dosing. For post-dose pharmacokinetic assessment, total 19 samples were collected at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 11.75, 12.50, 13, 13.50, 14, 15, 17, 20, 22, and 24 hours in each study period. Further total of 21 samples were collected at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 11.75, 12.50, 13, 13.50, 14, 15, 17, 20, 22, 24, 48, and 72 hours post-dose for pharmacodynamic assessment. On day 7, subjects left the facility after the 24-hour sample was taken. The post-dose blood samples at 48- and 72 hours were collected ambulatory (i.e., on separate visits). The samples were centrifuged at 3800 rpm for 10 minutes at 10 °C to separate plasma. Samples were divided into two aliquots and stored at -70 ± 10°C until analysis. Plasma samples were analyzed using a validated liquid chromatography-tandem mass spectrometry method.

Statistical analysis

The pharmacokinetic and pharmacodynamic statistical analysis was performed using SAS version 9.4.

Pharmacokinetic analysis

The primary pharmacokinetic parameter evaluated was the area under the concentration-time curve for one dosing interval at steady-state (AUC_{0- τ , ss}). The secondary pharmacokinetic parameter included maximum plasma concentration at steady state (C_{max, ss}), time until C_{max, ss} is reached (T_{max, ss}), and percentage fluctuation during steady state. Analysis of variance (ANOVA) was performed on the logarithmically (Ln) transformed values of the primary pharmacokinetic metrics. The F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (alpha=0.05). The two preparations were considered bioequivalent if the 90% confidence intervals (CIs) of the geometric mean ratios (test/reference) for Ln-transformed AUC_{0- τ , ss} were within the predefined acceptance range of 80–125%. Intra-subject coefficient of variation (ISCV) of the AUC_{0- τ , ss} was estimated

using the root mean square error obtained after using ANOVA for bioequivalence assessment.

Pharmacodynamic analysis

The pharmacodynamic parameters included percent DPP-4 inhibition and weighted average percent DPP-4 inhibition. Percent inhibition of DPP-4 was calculated as $100 \times (1 - \text{DPP-4 activity (t)} / \text{DPP-4 activity (0)})$, where DPP-4 activity (t) was the activity measured post-dose at time t and DPP-4 activity (0) was the enzyme activity measured pre-dose in the same treatment period. DPP-4 weighted average inhibition values were calculated by dividing the AUC for DPP-4 inhibition over 0-24 hours by 24. The ANOVA, 90% CIs using two one-sided tests, power, and ratio analysis were performed on Ln-transformed pharmacodynamic parameter percent DPP4 inhibition (0-24 hrs). The acceptance criterion was percent DPP-4 inhibition not less than 80% over 24 hours. ISCV of the percent DPP-4 inhibition was estimated using the root mean square error obtained after using ANOVA for bioequivalence assessment.

Safety evaluation

Safety assessment was based on clinical laboratory evaluation, chest X-ray (P/A view), ECG recordings, clinical examination along with vital signs (axillary temperature, radial pulse rate, sitting blood pressure, and respiratory rate) measurement, blood glucose monitoring and post-study clinical laboratory safety evaluation. Clinical examination, vital signs, and questioning for well-being were performed during screening, check-in, and before check-out of each period.

Ethical standards

The study was conducted following the ethics committee-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), GSR 227(E) New Drugs and Clinical Trials Rules, 2019 and Guidelines for Bioavailability and Bioequivalence Studies, Central Drugs Standard Control Organization, March 2005.

RESULTS

Subject disposition

The general screening was carried out within 21 days before dosing. Forty-two eligible subjects were enrolled in the study; During period 1, 42 subjects were dosed, and 40 were dosed in period 2. A total of 40 subjects were included in the final pharmacokinetic, pharmacodynamic, and statistical analysis. All subjects who had received at least one dose of the investigational product were included in the safety evaluation (Figure 1). The mean \pm standard deviation (SD) demographic details of the population considered for statistical evaluation were as follows: age 30.6 ± 5.88 years, height 168.5 ± 5.69 cm, weight 68.29 ± 9.22 kg, and BMI 24.06 ± 3.05 kg/m². All subjects were males of Asian origin, non-vegetarian, non-smokers, and non-alcoholic (Table 1).

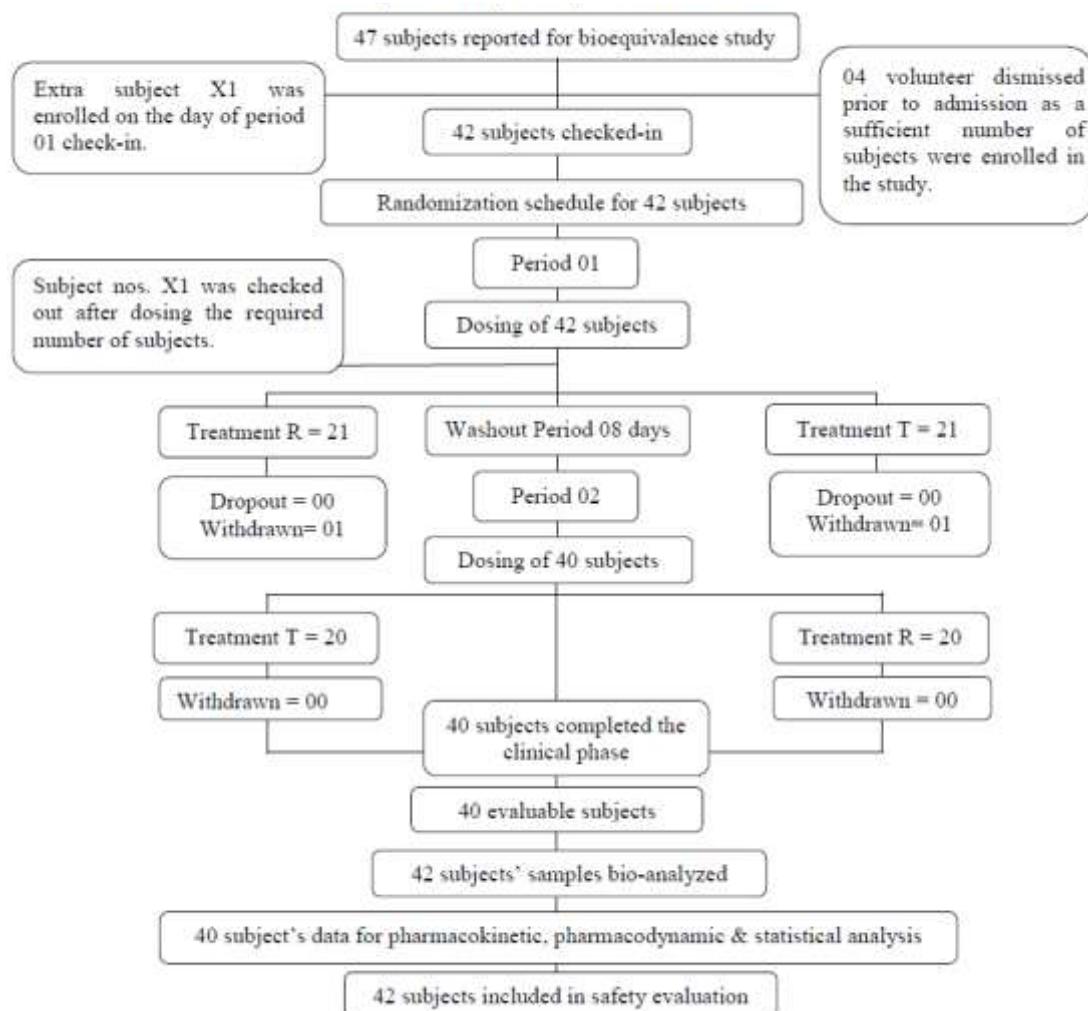


Figure 1: Subject Disposition Flowchart

Table 1: Demographic profile of the population considered for statistical evaluation (n = 40)

Parameter	Mean	SD	Mini	Max
Age (yrs)	30.6	5.88	19	41
Height (cm)	168.5	5.69	152	179
Weight (Kg)	68.29	9.22	52.05	91
BMI (Kg/m ²)	24.06	3.05	18.56	29.62

BMI: Body mass index; Mini: Minimum; Max: Maximum; SD: Standard deviation.

Pharmacokinetics

The key pharmacokinetic parameters of the test and reference product are summarized in Table 2. At steady state, the daily exposure provided by vildagliptin SR 100 mg tablet administered once daily was not significantly different from

the same daily dose of vildagliptin 50 mg tablet, administered twice daily. The mean \pm SD AUC_{0- τ} , ss values were 2689.06 \pm 835.47 ng.hr/mL for the test formulation and 2875.57 \pm 703.85 ng.hr/mL for the reference formulation. The median T_{max}, ss was 5 hours for the reference product and 13.5 hours for the test product.

Table 2: Pharmacokinetic parameters of test and reference vildagliptin of un-transformed data (n= 40) (Values are expressed as mean \pm SD unless otherwise indicated)

Pharmacokinetic parameters (Units)	Test product*	Reference product**
AUC _{0-τ} , ss (ng.hr/mL)	2689.06 \pm 835.47	2875.57 \pm 703.85
C _{max} , ss (ng/mL)	332.82 \pm 82.68	363.17 \pm 95.34
% Fluctuation	305.86 \pm 65.34	297.4980 \pm 59.8012
T _{max} , ss (hr)		
Median	5	13.5
Range	1.5-6	1-15

*Vildagliptin SR 100 mg tablet; **Vildagliptin 50 mg tablet;
AUC_{0- τ} , ss: Area under the concentration-time curve for one dosing interval at steady-state; CIs: Confidence intervals; C_{max}, ss: Maximum plasma concentration at steady state, SD: Standard deviation; T_{max}, ss: Time to observe maximum drug concentration in plasma at steady state.

The mean plasma concentration–time curves for both formulations are shown in Figure 2.

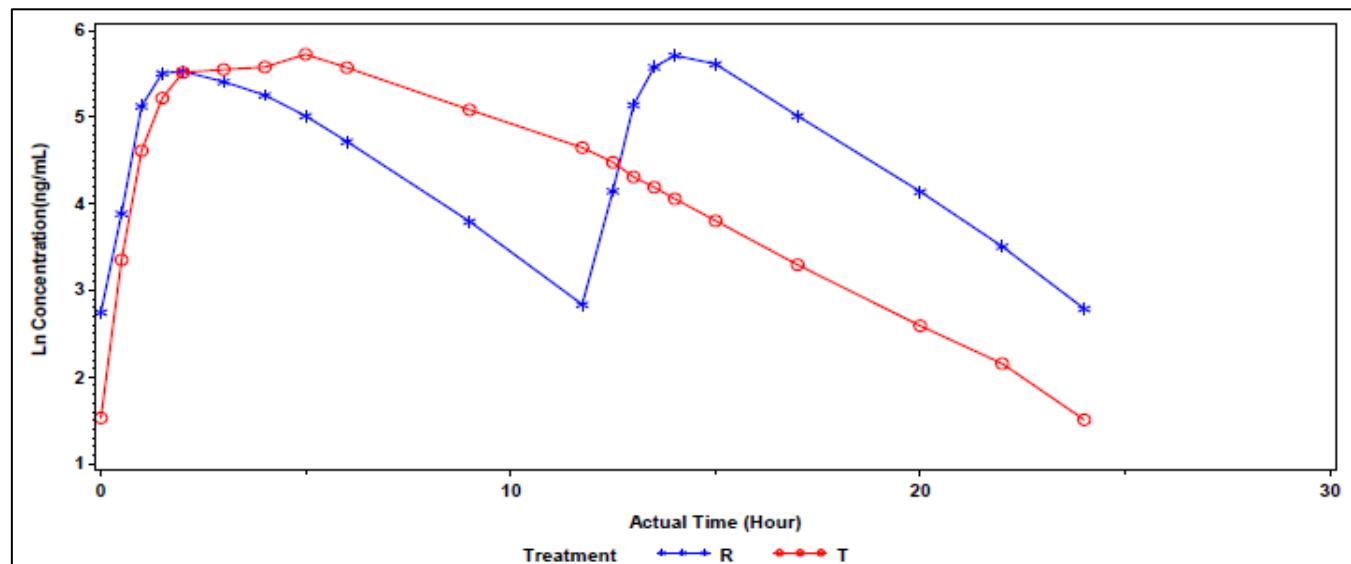


Figure 2: Mean plasma concentrations of vildagliptin vs. actual time for test product (T) and reference product (R) on day 07

As presented in Table 3, the ratios of geometric least squares mean of the test and reference products for the Ln-transformed pharmacokinetic parameters AUC_{0- τ} , ss of vildagliptin was 91.63%. The 90% CIs for the ratios of geometric least square means for the Ln-transformed pharmacokinetic parameters AUC_{0- τ} , ss of vildagliptin were

found to be 86.32% - 97.26%, well within the predefined bioequivalence limit of 80–125%. No statistically significant sequence or period effects were observed for the Ln-transformed AUC_{0- τ} , ss. However, statistically significant formulation effects ($p < 0.05$) were observed for the Ln-transformed AUC_{0- τ} , ss.

Table 3: Treatment ratios of the Ln-transformed geometric mean pharmacokinetic parameters of the test and reference vildagliptin formulations (n = 40)

Pharmacokinetic parameters (Units)	Geometric Least Squares Mean		T/R (%)	90% CIs	ISCV (%)	Power (%)
	Test Product* (T)	Reference Product** (R)				
AUC _{0-t} , ss (ng.hr/mL)	2802.36	2567.67	91.63	86.32-97.26	15.93	99.99

*Vildagliptin SR 100 mg tablet; **Vildagliptin 50 mg tablet; AUC_{0-t}, ss: area under the concentration-time curve for one dosing interval at steady-state; CIs: Confidence interval; ISCV: Intra-subject coefficient of variability.

Pharmacodynamics

Administration of multiple doses of vildagliptin SR 100 mg tablet and vildagliptin 50 mg tablet provided greater than 90% inhibition of DPP-4 activity in healthy subjects under fed conditions (Figure 3).

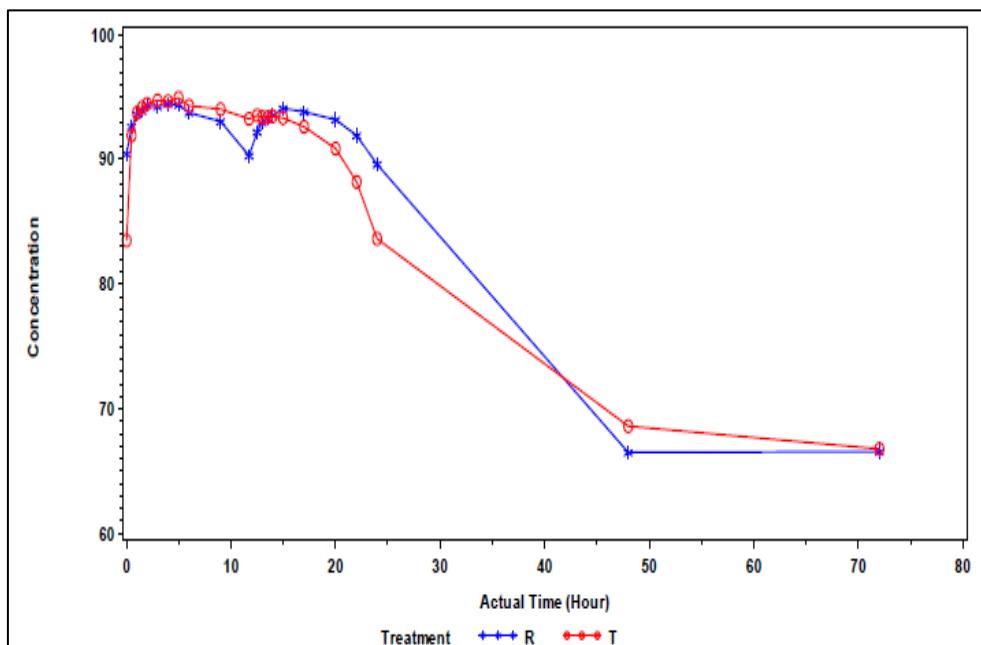


Figure 3: Mean comparative linear plot of percent DPP-4 inhibition on day seven after oral test product administration* (T) Vs. reference product** (R) (n = 40). *Vildagliptin SR 100 mg tablet; **Vildagliptin 50 mg tablet.

The study achieved the primary objectives of duration and weighted average percent DPP-4 inhibition above 80% over 24 hours post-dose for the test product on day 7. The weighted average percent DPP-4 inhibition (0-24 hrs) was

92.66% with vildagliptin SR 100 mg tablet and 93.26% with vildagliptin 50 mg tablet, respectively (Figure 4). The ISCV for percent DPP-4 inhibition (0-24 hrs) was 15.93%.

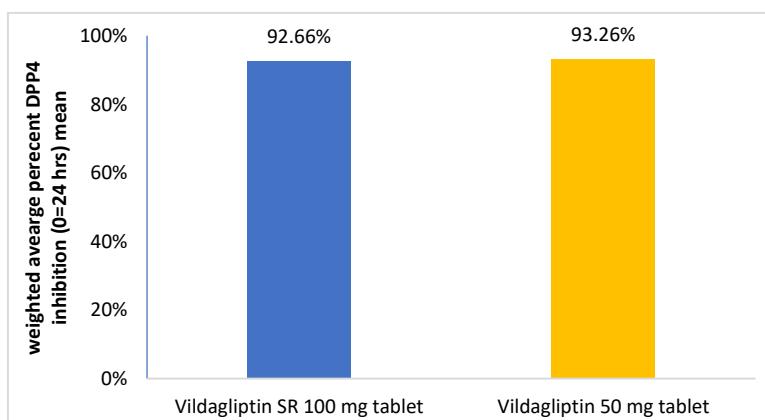


Figure 4: Weighted average percent DPP-4 inhibition 0-24 hrs after oral administration of vildagliptin SR 100 mg tablet and vildagliptin 50 mg tablet (n=40)

For percent DPP-4 Inhibition, the geometric least square mean ratio was 93.01%, and 90% CI obtained (0-24 hrs) based on Ln-transformed data of vildagliptin is 89.99%-96.12%. The

power value obtained for percent DPP-4 inhibition (0-24 hrs) was 100% (Table 4).

Table 4: Treatment ratios of the Ln-transformed geometric mean pharmacodynamic parameters of the test and reference vildagliptin formulations (n = 40)

Pharmacokinetic parameters	Geometric Least Squares Mean		T/R (%)	90% CIs	Power
	Test Product* (T)	Reference Product** (R)			
Percent DPP-4 inhibition	89.35	83.10	93.01	89.99 - 96.12	100%

*Vildagliptin SR 100 mg tablet; **Vildagliptin 50 mg tablet; CIs: Confidence intervals; DPP-4: Dipeptidyl-peptidase-4

Safety and tolerability

Both test and reference products were generally well-tolerated during the entire study period. No serious or life-threatening adverse events (AEs) were reported during the study. The incidence of AEs, both overall and investigational product-related, was low for both parts of the study. A total of 4 AEs were reported during the study. One AE occurred in period one and three AEs during the post-study clinical

laboratory safety evaluation. One subject suffered from hypertension after administration of the reference product during period 1. A clinically significant laboratory abnormality detected during the post-study clinical laboratory safety evaluation was increased direct bilirubin. These AEs were detected during the end-of-study safety analysis and could not be attributed to the test or the reference product. All AEs were graded as 'mild' in intensity and 'unlikely' related to investigational products (Table 4).

Table 5: Adverse events recorded

Adverse event	Treatment	Intensity	Relationship to drug
Hypertension	Reference product	Mild	Unlikely
Increased direct bilirubin	Test and/or reference product	Mild	Unlikely
Increased direct bilirubin	Test and/or reference product	Mild	Unlikely
Increased direct bilirubin	Test and/or reference product	Mild	Unlikely

DISCUSSION

Vildagliptin is an effective and safe DPP-4 inhibitor as monotherapy and in combination with other antidiabetic medications.⁹ It is weight-neutral, has a low risk of hypoglycemia, and carries no extra risk of harmful cardiovascular effects. Vildagliptin can be used to manage patients with newly diagnosed diabetes and those with chronic disease.⁵ Results of randomized controlled trials demonstrated that oral vildagliptin improves glycemic control in the elderly and in patients with moderate to severe renal impairment.¹⁰ Hence, oral vildagliptin is a valuable option in managing T2DM.

The bioequivalence of extended-release dosage forms should be preferably assessed under steady-state after multiple doses rather than single-dose conditions, as there is a greater likelihood that the drug products will be therapeutically equivalent, especially when there is a substantial accumulation of the drugs.¹¹ Our study was also conducted to characterize the test formulation's steady-state pharmacokinetic and pharmacodynamic profile compared to the reference formulation. Findings from the study demonstrated the bioequivalence of vildagliptin SR 100 mg tablet and vildagliptin 50 mg tablet in healthy male subjects under fed conditions. At usual prescribed doses, i.e., vildagliptin SR 100 mg once daily and vildagliptin 50 mg twice daily yielded a similar pharmacokinetic profile. The AUC_{0- ∞} , ss, and other evaluated pharmacokinetic parameters, like C_{max}, ss, and % fluctuation, were comparable. The 90% CIs of the geometric least-squares mean ratios of the test and reference product for AUC_{0- ∞} , ss were within prespecified

bioequivalence limits of 80 - 125%. In addition, vildagliptin SR tablet 100 mg and vildagliptin 50 mg tablet showed above 80% DPP-4 inhibition for 24 hours on day 7. Both formulations were well tolerated, with no serious AEs. The total incidence of AEs was not different between the formulations.

Similar to this, a study by Joshi et al under fasting conditions showed that vildagliptin SR 100 mg is bioequivalent to vildagliptin 50 mg and provides 80% DPP4 inhibition for 24 hours, thus improving glycemic control while decreasing the frequency of medication intake.¹² Evidence suggests that vildagliptin SR 100 mg once daily is equally efficacious and safe as vildagliptin 50 mg twice daily. The result of a randomized, open-label, phase 4 and clinical trial conducted on Indian patients showed that vildagliptin 100 mg SR once daily is equally effective as 50 mg twice daily vildagliptin in reducing HbA1C, fasting, and postprandial blood glucose levels when used along with metformin. Both the drugs were equally safe in terms of changes in liver enzymes and serum bilirubin.¹³

The findings of our study can be used for bioequivalence and pharmacokinetic profiling of vildagliptin SR; however, it is warranted to investigate further longer duration of drug administration from multicenter study and monitoring of potential AEs.

CONCLUSION

In healthy adult subjects under fed conditions, vildagliptin SR 100 mg showed similar pharmacokinetic and pharmacodynamic profiles as vildagliptin 50 mg. They were

both bioequivalent. Additionally, the duration and weighted average percent inhibition of DPP-4 with vildagliptin SR 100 mg tablet exceeded 80%. The tolerability and safety profiles were similar for both products. In conclusion, vildagliptin SR 100 mg tablet is expected to provide similar therapeutic benefits as vildagliptin 50 mg tablet with less frequent dosing leading to better patient compliance.

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