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Research Article

A comparative pharmacodynamic and pharmacokinetic study of Vildagliptin SR 100 mg tablet in normal healthy adult male subjects

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Abstract

Background: Vildagliptin, a potent dipeptidyl peptidase IV inhibitor (DPP-4i), is usually administered twice daily to provide ≥90% inhibition of DPP-4 over 24 hours. Considering most type 2 diabetes (T2D) patients are on multiple medications, reducing dosing and pill burden can increase patient convenience. A 100 mg Vildagliptin sustained release (SR) formulation that would inhibit DPP-4 ≥ 80% over 24 hours with a lower dosing frequency was developed. The study was thus conducted to evaluate the pharmacodynamics, pharmacokinetics, and safety profile of once-daily Vildagliptin SR compared to twice-daily Vildagliptin immediate-release (IR) formulation.

Results: Twenty-four healthy adult male subjects were enrolled, and 22 completed the clinical phase of the study. The DPP-4 inhibition over time was comparable between the formulations. At 24 hrs single dose of once-daily Vildagliptin SR 100 mg tablet inhibited DPP4 by 89.58%, whereas twice-daily Vildagliptin IR 50 mg by 91.052%. The pharmacokinetic parameters like peak plasma concentration (C_{max}), area under the plasma concentration-time curve from 0 hours to the last measurable concentration (AUC_{0-t}) and AUC-time curve up to infinity (AUC_{0-inf}) were not significantly different in both groups. Besides this, both groups reported no serious adverse effects during the study period.

Conclusion: The above result shows that once-daily Vildagliptin SR 100 mg is bioequivalent to twice-daily Vildagliptin IR 50 mg. Moreover, the ability of Vildagliptin SR 100 mg to provide above 80% DPP-4 inhibition coverage over 24 hrs may help to achieve a clinically meaningful glucose-lowering effect and reduce the pill burden in diabetes patients.

Keywords: Vildagliptin, dipeptidyl peptidase IV inhibitor (DPP-4i), type 2 diabetes (T2D) patients, pharmacokinetic parameters

BACKGROUND

Dipeptidyl peptidase IV inhibitors (DPP-4i) are an increasingly well-recognized class of oral antidiabetic medications for treating type 2 diabetes (T2D).[1] One of the widely used potent DPP-4i is Vildagliptin. It is recommended for patients with poorly controlled glycemia alone or combined with another antidiabetic monotherapy. Vildagliptin is available as a 50 mg immediate-release (IR) tablet. The 50 mg single-dose Vildagliptin exhibits ≥80% inhibition of DPP-4 for 12 hours (hrs) post-dose, while the 100 mg single bolus dose exhibits ≥80% inhibition for approximately 15-16 hours. As a result, it is recommended to use Vildagliptin 50 mg twice-daily (BD) to provide ≥90% inhibition of DPP-4 over 24 hours.[2] Patients with T2D, due to the progressive nature of the disease, often require multiple oral hypoglycemic agents and add on insulin therapy as monotherapy or as part of polytherapy. A considerable amount of evidence indicates that polytherapy and multiple daily dosage schedules decrease patient adherence.[3]

With modern advances in oral formulation technologies, newer dosage forms of existing medications can be developed that reduce dosing frequency while maintaining therapeutic efficacy.[2] The sustained release (SR) formulations are designed to achieve a prolonged therapeutic effect by continuously releasing medication over a long time after administering a single drug dose. They offer multiple advantages like reduction in the frequency of intakes, reduced side effects, the uniform release of drugs over time, and better patient compliance.[4] A matrix system is commonly used for SR formulations. It helps to prolong and control the release of dispersed or dissolved drugs. Matrixes are composed of one or more drugs mixed with gelling agents, such as hydrophilic polymers.[5] Utilizing the polymer matrix SR coating, Vildagliptin SR 100 mg tablet formulation was developed, allowing a once-daily (OD) administration.[6] This can be a practical therapeutic alternative to the twice-daily Vildagliptin IR 50 mg dose.

A current study compared the pharmacodynamics, pharmacokinetics, and safety of a single oral dose of once-daily Vildagliptin SR 100 mg tablets with twice-daily Vildagliptin IR 50 mg tablet in healthy adult male subjects.

METHODS

- **Subjects**

The study was conducted on 24 healthy adult male subjects willing to consent. The subjects' ages were between 18 to 45 years (inclusive), and their body mass index (BMI) was

between 18.0 to 25.0 kg/m^2. All the subjects had no medical history of significant diseases or clinically significant abnormal findings during the pre-study screening, physical examination, and laboratory evaluations.

- **Study design**

A single-center, randomized, open-label, analyst-blind, two-treatment, two-period, two-sequence, and crossover study designed to evaluate and compare pharmacokinetics /pharmacodynamics and safety profiles of single dose Vildagliptin SR 100 mg OD tablet [Manufactured by Exemed Pharmaceuticals, Gujarat, India] with two tablets of Jalra IR 50 mg (Vildagliptin 50 mg) (twice a day) [Manufactured by MSN Laboratories Pvt. Ltd, India] in normal healthy, adult male subjects under fasting condition.

The duration of the clinical phase was 12 days, including 7 days washout period between each dosing period. The subjects who received test (or reference) treatment in the period I was given reference (or test) treatment in Period II. Subjects were fasted for at least 10 hours before drug administration and 4 hours post-dose in each study period. They were then administered either a single oral dose of one tablet of the test product Vildagliptin SR 100 mg tablet or two tablets of the reference product – Vildagliptin IR 50 mg (one tablet at an interval of 12 hours). Assigned drug treatment was given to all subjects in a sitting posture along with 240 mL of 20% glucose solution.

- **Objective**

The study's primary objective was to evaluate the pharmacodynamics of Vildagliptin SR 100 mg tablet in terms of duration of DPP-4 inhibition above 80% over 24 hours post-dose. The secondary objective was to evaluate its pharmacokinetic parameters, safety, and tolerability.

- **Statistical analysis**

Statistical analysis was done using SAS® and WinNonlin software.

Pharmacodynamic (PD) analysis

PROC GLM was used to estimate the least square mean (LSM) differences (Test-Reference) of the test and reference formulation on the log-transformed percent (%) DPP-4 inhibition of Vildagliptin. The analysis of variance (ANOVA), equivalent to two one-sided tests, was performed on log-transformed % DPP-4 inhibition of Vildagliptin, and 90% confidence intervals (CI) were constructed for the LSM (Test-Reference) of the log-transformed % DPP-4 inhibition of Vildagliptin. For the % DPP 4 inhibition of Vildagliptin, 90 % CI for the test and reference product averages ratios was calculated using the error variance obtained from the ANOVA.

The % inhibition of DPP-4 was calculated as 100 X (1 - At/A0), where A0 is the enzyme activity measured pre-dose and the activity measured post-dose at time t in the same treatment period.

***Pharmacokinetic (PK)* analysis**

A validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) bioanalytical method analyzes plasma samples for the concentration of Vildagliptin. The log-transformed pharmacokinetic parameters peak plasma concentration (C_{max}), area under the plasma concentration-time curve from 0 hours to the last measurable concentration (AUC_{0-t}), and AUC-time curve up to infinity (AUC_{0-inf}) of Vildagliptin were analyzed using an ANOVA model with the main effect of treatment, period, and sequence as fixed effect and subject nested within the sequence as a random effect. Statistical analysis was performed using SAS® software. ANOVA, two one-sided tests for bioequivalence, and ratio analysis for log-transformed pharmacokinetic parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} of Vildagliptin were performed. Bioequivalence was concluded if the CI so constructed falls within the acceptance range of 80- 125 % for Ln-transformed Cmax, AUC0-t, and AUC0-inf of Vildagliptin.

Safety evaluation

Safety measurements included monitoring of adverse events, physical examination, recording of vital signs, and clinical laboratory tests before, during, and post-study.

RESULTS

A total of 22 subjects completed the clinical phase of the study successfully. Samples of these subjects were analyzed and considered to draw a statistical conclusion.

Pharmacodynamic results

For DPP-4 analysis a total of 22 blood samples (3 mL each) were taken per period in vacutainers with gel and clot activator, at pre-dose (within 01.00 hrs prior to dosing) and at 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 9.00, 11.75, 12.50, 13.00, 13.50, 14.00, 15.00, 17.00, 20.00, 22.00, 24.00, 48.00 and 72.00 hours post dose.

The study achieved primary objectives in terms of duration of % DPP-4 inhibition above 80% over 24 hours post-dose for the test product. Both once-daily Vildagliptin SR and twice-daily Vildagliptin IR demonstrated more than 80% DPP-4 inhibition till 24 h post-first dose. The DPP4 inhibition at 24 hrs was 89.58% with a single-dose of once-daily Vildagliptin SR 100 mg tablet vs. 91.05% with twice-daily Vildagliptin IR 50 mg **(Figure 1)**.

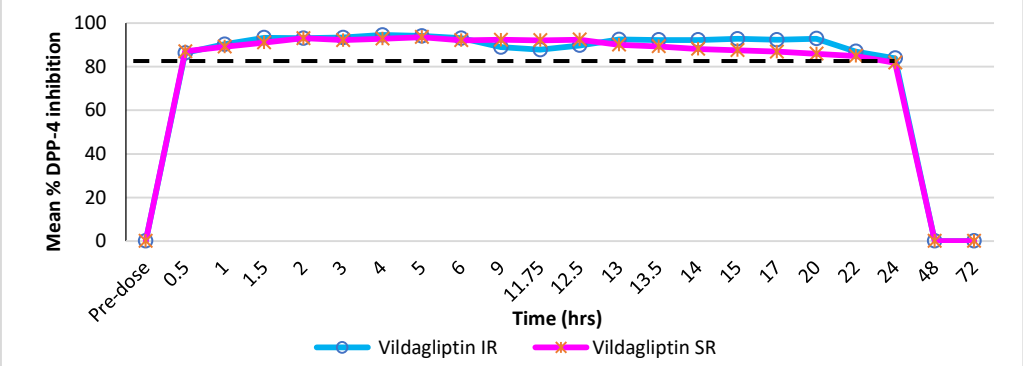

Figure 1: Mean % DPP-4 inhibition profile of Vildagliptin IR (BD) and Vildagliptin SR (OD) over 24 hrs after single dosage administration

The geometric LSM ratio and 90% CI obtained for % DPP-4 Inhibition (0-24 hrs) based on log-transformed data of Vildagliptin are as follows: 98.38 % (97.36 % - 99.42 %) (Table 1). The coefficient of variation (CV%) corresponding to intra-subject variability for % DPP-4 inhibition (0-24 hrs) was 2.02 %. The power value obtained for % DPP-4 inhibition (0-24 hrs) was 100 %.

Table 1: Percentage DPP- 4 inhibition (0-24 hrs) based on log-transformed data

Geometric mean		% Ratio	90% CI for log-transformed	
Vildagliptin SR Test (T)	Vildagliptin IR Reference (R)	T/R	Lower limit	Upper limit
89.582	91.052	98.38	97.36	99.42

CI, confidence interval; DPP-4, dipeptidyl peptidase IV

Pharmacokinetic results

A total of 22 blood samples (3 mL each) were taken per period in K3EDTA vacutainers, at pre-dose (within 01.00 hrs prior to dosing) and at 0.50, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 9.00, 11.75, 12.50, 13.00, 13.50, 14.00, 15.00, 17.00, 20.00, 22.00, 24.00, 48.00- and 72.00-hours post-dose. The mean pharmacokinetic parameters estimated for 22 completed subjects for both the test and reference product are summarized in **Table 2**.

Table 2: Mean pharmacokinetic parameters

Pharmacokinetic parameters		Vildagliptin SR	Vildagliptin IR
Cmax (ng/mL)	Mean ±SD	235.480 ±70.924	237.359±48.971
AUC_{0-t} (ng*hr/mL)	Mean ±SD	2009.286±683.799	2033.257 ±539.013
AUC_{0-inf} (ng*hr/mL)	Mean ±SD	2074.773±704.190	2080.756 ± 568.821
T_{max} (hrs)	Mean ±SD	5.00 (median) ± 0.79	2.00 (median) ± 4.96
T1/2 (hrs)	Mean ±SD	3.82 ± 1.92	2.08 ± 0.51

AUC_{0-t}, plasma concentration-time curve from 0 hours to the last measurable concentration; AUC_{0-inf}, plasma concentration-time curve up to infinity; C_{max}, peak plasma concentration; T_{max}, time to reach C_{max}; $T_{1/2}$, terminal elimination half-life; SD, standard deviation

The mean plasma drug concentration profiles of both the Vildagliptin dosage are depicted in **Figure 2**.

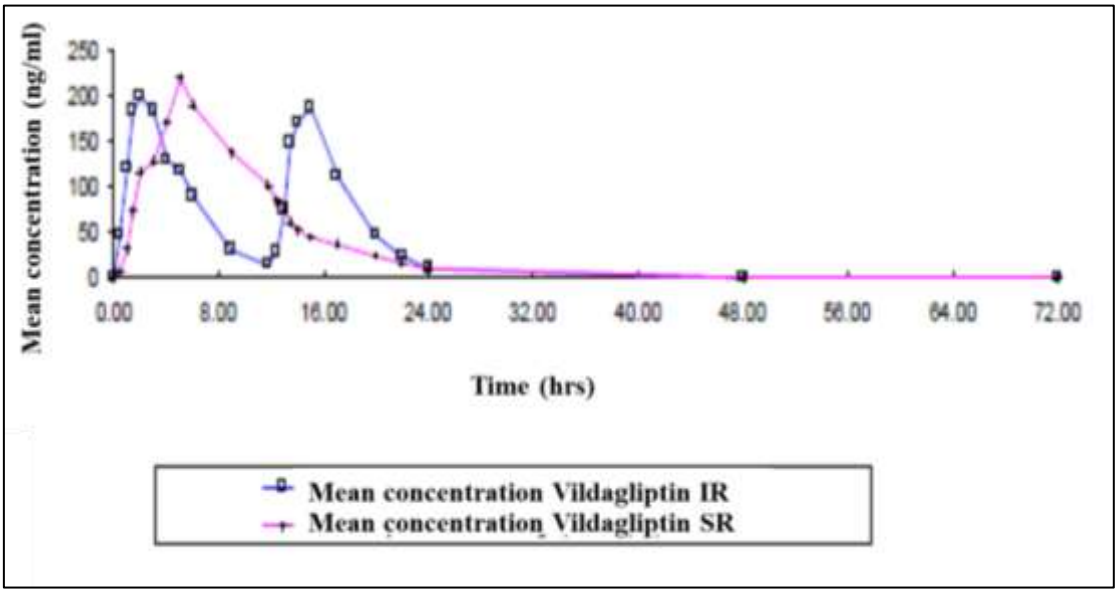

Figure 2: Mean plasma concentration vs. time profiles of Vildagliptin IR (BD) and Vildagliptin SR (OD) after single dosage administration

The ratios of geometric LSM and its 90% CI on the log-transformed pharmacokinetic Cmax, AUC0-t, and AUC0-inf of both Vildagliptin formulations were within the acceptance criteria of 80% to 125%. In ANOVA analysis, no significant sequence, period, and treatment effect was observed for log-transformed Cmax, AUC0-t, and AUC0-inf of Vildagliptin (Table 3).

Table 3: Geometric mean, 90% CI, and ANOVA analysis of the log-transformed parameters of Vildagliptin

	C_{max}	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$
Geometric mean for Vildagliptin SR test (T) product	224.709	1880.075	1941.259
Geometric mean for Vildagliptin IR reference (R) product	231.498	1957.874	1999.726
% Ratio (T/R)	97.07	96.03	97.08
90 % Cl (T vs. R) lower Limit	84.55	80.69	81.54
90 % CI (T vs. R) upper limit	111.44	114.28	115.57
ANOVA p-value			
Sequence	0.7370	0.7588	0.7786
Period	0.6529	0.7513	0.8260
Treatment effect	0.7139	0.6921	0.7721

ANOVA, analysis of variance; AUC0-t, plasma concentration-time curve from 0 hours to the last measurable concentration; AUC 0-inf, plasma concentration-time curve up to infinity; CI, confidence interval; Cmax, peak plasma concentration.

Safety results

Both the formulations were safe and well tolerated by the subjects under fasting conditions. No adverse event or serious adverse event was observed during the study periods.

DISCUSSION

This study compared the pharmacokinetic-pharmacodynamic characteristics of once-daily Vildagliptin 100 mg SR tablets to the marketed twice-daily 50 mg IR formulation. Vildagliptin IR 50 mg is typically prescribed for the clinical management of T2D as a monotherapy or in combination with other antihyperglycemic agents. One of the reasons for poor adherence to T2D is the complexity of medication regimens and pill burden. The studies have shown that SR formulations provide an appropriate option for patients with T2D who require several medications to achieve glycemic control or manage comorbid conditions and for those who have an intolerance to the IR formulation.[7,8]

As per the available data, gliptins' average DPP-4 inhibition over 24 hours must exceed 70% to demonstrate clinically significant glucose lowering benefits.[2] Additionally, it has been shown that DPP-4 inhibition of >80% increases active glucagon-like peptide-1 and gastric inhibitory polypeptide levels by 2-fold, resulting in near-maximal decreases in plasma glucose levels. [9] This study reported DPP-4 inhibition above 80% for 24 hours with both once-daily Vildagliptin SR 100 mg tablets and twice-daily Vildagliptin IR 50 mg tablets. Single-dose of once-daily Vildagliptin SR 100 mg tablet showed 81.83% DPP-4 inhibition at 24 hrs. Based on log-transformed Vildagliptin data, the geometric LSM ratio and 90% CI for % DPP-4 Inhibition (0-24 hrs) was 98.38 % (97.36 % - 99.42 %). Hence the study was able to achieve the primary objectives.

Overall, the pharmacokinetic parameters were comparable. No significant sequence, period, and treatment effects were observed between once daily Vildagliptin SR 100 mg tablets and twice daily Vildagliptin IR 50 mg tablets. Compared with the Vildagliptin IR, the Vildagliptin SR tablet exhibited a slight reduction in C_{max} and overall drug exposures (AUC_{0-t} and AUC_{0-inf}) with increased T_{max} and $T_{1/2}$. These distinct pharmacokinetic characters confirm the sustained-release nature of the test product. No serious adverse events were reported during the study periods, highlighting the good safety profile of both Vildagliptin SR 100 mg and vildagliptin IR 50 mg tablet.

CONCLUSION

This study confirms the bioequivalence of once-daily Vildagliptin SR 100 mg to twice-daily Vildagliptin IR 50 mg. Both the formulations were therapeutically equivalent in inhibiting DPP-4 over time. Thus, above 80% DPP-4 inhibition over 24 hrs by Vildagliptin SR 100 mg tablet may offer clinically relevant glycemic control and improve treatment adherence and patient compliance. Besides this, Vildagliptin SR 100 mg tablet was safe and well-tolerated. To conclude, the study supports Vildagliptin 100 mg SR once daily as a valuable therapeutic alternative to Vildagliptin IR.

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List of Abbreviations

DPP4i- Dipeptidyl peptidase 4 inhibitors

SR= Sustained Release

IR= Immediate Release

PK=Pharmacokinetics

PD= Pharmacodynamics

C_{max}= Peak plasma concentration

AUC_{0-t}= Area under the plasma concentration-time curve from 0 hours to the last measurable concentration

AUC_{0-inf}= AUC-time curve up to infinity

T_{max}= Time to reach C_{max}

$T_{1/2}$=Terminal elimination half-life

SD= Standard deviation.

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