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Comparative Clinical Pharmacokinetics and Pharmacodynamics of Investigational Once-Daily Sustained-Release (SR) Vildagliptin 100 mg Tablet Formulation with Conventional 50 mg Twice-Daily Regimen in Healthy Indian Males

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ABSTRACT: Background- Among the gliptins, vildagliptin is the only therapy requiring twice-daily dosing and thus adversely impacts patient adherence. To reduce dosing frequency, we developed a once-daily sustained-release (SR) vildagliptin 100 mg tablet formulation with potential to furnish comparable dipeptidyl peptidase-4 (DPP-4) inhibition coverage to the conventional twice-daily regimen.

Objective- The current study compares the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of investigational once-daily SR vildagliptin 100 mg tablet formulation with the twice-daily dosage of marketed product, Galvus® in healthy Indian adult males after single and multiple-dose administration.

Methods- Single and multiple-dose PK-PD assessment was conducted in separate clinical studies enrolling thirty-six healthy subjects under fed-condition. Each study was a randomized, open-label, two treatment, two-period, crossover design. Drug plasma concentrations were quantified by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. DPP-4 inhibition was estimated in the fluorescence-based assay. PK parameters were calculated from the plasma concentration-time curve employing Phoenix® WinNonlin® software. Formulation safety was evaluated by monitoring adverse events.

Results- SR vildagliptin 100 mg tablet resulted in peak-less, nearly steady drug concentration-time profile. Thus, its mean PK characteristics after single [C_{max} (147.7), $AUC_{(0-24)}$ (1645.04), T_{max} (5.29 hr), $t_{1/2}$ (4.61 hr)] and multiple-dose [C_{maxss} (163.59), $AUC_{ss\ (0-24)}$ (1815.36), and T_{maxss} (4.65 hrs), $t_{1/2ss}$ (3.71 hr)] administrations were significantly distinct from the Galvus® twice-daily regimen. SR vildagliptin 100 mg tablet demonstrated more than 80% DPP-4 inhibition profile for approximately 23 hrs in both the studies which was comparable to Galvus® twice-daily regimen.

Conclusions- Investigational SR vildagliptin 100 mg tablet formulation was found to be safe and well-tolerated. Its ability to provide nearly 80% DPP-4 inhibition coverage over 23 hrs post-dose may reduce the additional pill burden in patients on conventional twice-daily regimen.

KEYWORDS: Healthy Volunteers, Once-Daily, SR Vildagliptin 100 mg, Pharmacokinetics, Pharmacodynamics.

1. INTRODUCTION

Proceeding rise in type-2 diabetes (T2D) patient population size is a serious global healthcare concern [1]. Impaired glucose homeostasis in T2D patients is a collective consequence of the deterioration of insulin secretion and peripheral insulin resistance [2]. The gastrointestinal incretin hormone, glucagon-like peptide-1 (GLP-1) is known to promote the majority of the post-prandial insulin secretion [3]. However, biological half-life of this endogenous peptide is very short (approximately 2 mins) due to rapid degradation from the ubiquitous enzyme, dipeptidyl peptidase-4 (DPP-4) [4]. The 'Gliptin or DPP-4 inhibitor' class of drugs address this issue by preventing GLP-1 degradation and elevating its bioavailability to potentiate glucose-stimulated insulin secretion.

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Unlike, sulfonylureas and biguanides they do not cause hypoglycaemia or weight-gain complications. As a result, several DPP-4 inhibitors are currently available as a regulatory approved therapy [5-7].

Among the gliptins, vildagliptin is a competitive, reversible DPP-4 inhibitor [8, 9]. This potent, orally-active small-molecule is currently being prescribed in more than 125 countries [10] as a 50 mg immediate-release (IR) tablet formulation [11]. Vildagliptin is recommended as a mono or combination therapy in patients with poorly controlled glycaemia either by diet, exercises alone or using other anti-diabetic monotherapy [11]. Single-dose of 50 mg vildagliptin is known to elicit ≥80% DPP-4 inhibition for 12 hours (hrs) post-dose [12, 13] while 100 mg single bolus dose is reported to exhibit ≥80% DPP-4 inhibition for approximately 15-16 hrs [13]. Therefore, to provide the maximal (≥80%) DPP-4 inhibition coverage over 24 hrs, vildagliptin 50 mg twice-daily (BID) dose is clinically recommended [11].

Mostly, it is observed that multiple-daily oral dosing is negatively associated with patient medication adherence. Thus, reducing dosage frequency to once-a-day (OD) is advocated to improve patient compliance to any pharmacotherapy [14, 15]. Recent advances in oral formulation technologies allow the development of newer dosage forms of existing medications to reduce dosing frequency by altering PK characteristics but retaining therapeutic efficacy. Osmosis-mediated oral drug delivery (OSMO) system offers zero-order drug kinetics, enabling the delivery of active drug constituents into the blood circulation at sustained therapeutic levels over an extended period to produce a prolonged pharmacological effect, hence allowing OD delivery of pharmacotherapy [16]. Utilizing the OSMO laser technology platform, we developed a push-pull osmotic pump (PPOP) bi-layer sustained-release (SR) vildagliptin 100 mg tablet formulation, allowing OD administration on account of its ability to furnish comparable DPP-4 inhibition coverage to the conventional 50 mg BID regimen. This unique tablet formulation is expected to improve patient compliance with therapy by minimising dosing frequency. Therefore, current clinical work was designed to establish the single and multiple oral dose PK/PD characteristics of investigational SR vildagliptin 100 mg tablet formulation in comparison with traditional 50 mg BID regimen in healthy Indian males.

2. METHODS

Both (single and multiple-dose) studies were conducted between January 2020 to July 2020 at Department of Clinical Pharmacokinetics & Biopharmaceutics (CPB), Wockhardt Research Centre, Aurangabad, India. The facility is approved by the Drugs Controller General of India (DCGI).

2.1 Subjects

Each, single and multiple-dose study planned to enrol 36 subjects. Normal, healthy Indian males of 18-45 years age (both inclusive) with bodyweight ≥50 kg and a body mass index (BMI) ranging between 18.5 and 30.0 kg/m^2 (both inclusive) were eligible for the study upon confirming their normal findings on laboratory tests (bilirubin, creatinine, amylase, urea, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT)), physical examination, abdomen ultrasonography (USG), and chest X-ray (postero-anterior view).

Standard exclusion criteria concerning alcohol or drug addiction, blood donation, caffeine intake, abnormal plasma glucose levels (fasting or post-meal), difficulty in swallowing, and participation in other studies were applied. Subjects with a prior history of allergy or hypersensitivity to vildagliptin, history of any psychiatric or metabolic disorder, impairment of renal/hepatic/ cardiac/neurological/lungs/gastrointestinal function were excluded. Subjects who understood and comply with the study procedures were checked in for the study. All participants were advised to refrain from taking any over-the-counter or prescription medication two weeks before initiation and during the study.

2.2 Study Design

A single-centre, randomized, open-label, analyst-blind, two-treatment, two-period, two-sequence and cross-over study was designed to evaluate single and multiple-dose PK/PD and safety profiles of investigational SR vildagliptin 100 mg tablet formulation (Wockhardt Limited, India; Batch No: NU10089; Mfg. Date:03-2019; Expiry Date: 02-2021) and marketed IR vildagliptin 50 mg tablet formulation (Galvus®) (Novartis Pharma, Switzerland; Lot No: JM9727; Mfg. Date: 10-2018; Expiry Date: 09-2021) under fed condition.

The primary objective of the study was to demonstrate the non-inferiority of investigational SR vildagliptin 100 mg OD regimen over BID dosage of Galvus® 50 mg IR in terms of weighted average DPP-4 inhibition till 24 hrs post-administration [WAI (0-24 h)]. The acceptance criterion for either formulation was to demonstrate WAI (0-24 h) above 80% upon single and multiple-dose (on

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Day-10) administration. The secondary objective was to evaluate its PK, safety and tolerability at total doses administered as OD versus (vs) BID during single-dose and multiple-dose study (consecutive 10 days).
Both the studies consisted of two treatment periods separated by at least seven days of a 'wash-out' phase. Each period assigned a total of 18 subjects to receive either formulation treatment in a cross-over fashion to expose a total of 36 participants for each treatment **(Fig. 1)**.

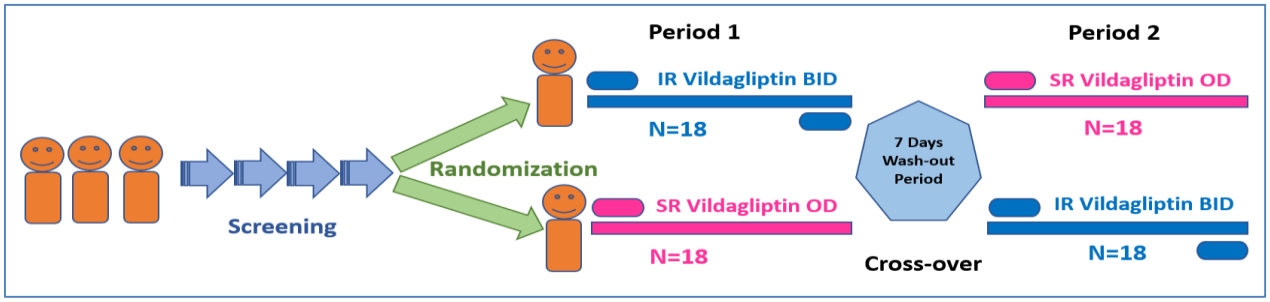

Fig. 1 Study design accessing single and multiple-dosage PK/PD characters of IR vildagliptin 50 mg (BID) and SR vildagliptin 100 mg (OD) tablet regimen

All subjects were admitted to the study facility one day before to each study period and received the assigned drug treatments in the morning (OD) or morning and evening (BID) on day 1 (single-dose study) or on days 1 to 10 (multiple-dose study). The morning dose was administered after 10 hrs of overnight fast, and the evening dose was administered approximately 12 hrs post-morning dose (2 hr before dinner). Assigned drug treatment was given to all subjects in a sitting posture along with 240 ± 02 mL of drinking water. The time of drug administration was recorded as the time at which the subject completed consumption of drinking water. All subjects were housed at the study facility till 24 hrs post-drug administration (for multiple-dose study, 24 hrs after Day-10 of treatment) and were instructed to return to the study site before the scheduled time for collection of 48 and 72 hrs post-dose ambulatory sample in each period. Identical, standardized meal (high-fat, high-calories), breakfast and snack were provided to all participants during each study period.

2.3 Pharmacokinetic Evaluations

Single and multiple-dose PK properties of both the tablet formulations were assessed by quantifying plasma vildagliptin concentrations in a validated LC-MS/MS (AB Sciex API 3000/4000) method. A blood sample (3-5 mL) was collected from all participants during each time-point in each study period via an indwelling catheter placed in the forearm vein. After centrifugation, plasma was separated and stored at -80°C until further analysis. Plasma samples were extracted using a solid-phase extraction technique (Oasis® HLB SPE Cartridge) on a positive pressure unit.
For a single-dose study, a total 20 blood samples were collected from each subject during each period at 0.00 hr (Pre-dose) 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 hrs post-dose. The pharmacokinetic parameters were calculated for every individual subject from the respective plasma concentration-time profile using the non-compartmental model of Phoenix® WinNonlin® version 6.4 (Certara, Princeton, NJ, USA). The PK parameters were maximum concentration (C_{max}), the area under the plasma concentration-time curve (AUC) from zero to 24 hrs concentrations (AUC_{0-24}), the time required to achieve maximal concentrations (T_{max}), and half-life ($t_{1/2}$).
Similarly, a total of 23 blood samples were collected from each participant in the multiple-dose study during each period. A total of 4 pre-dose samples were collected on Day-1, Day-8, Day-9 and Day-10 before administration of the morning dose. After Day-10 morning dose administration, blood samples were collected 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 and 24.00 hrs. The calculated PK parameters were maximum concentration at steady state (C_{maxss}), AUC to the end of the dosing period ($AUC_{0-\tau}$), the trough concentration ($C_{\tau ss}$), time to reach maximum plasma concentration at steady state (T_{maxss}), and half-life at steady state (T_{halfss}).

2.4 Pharmacodynamic Evaluations

PD profiles of both the treatment cohorts were determined by estimating plasma DPP-4 inhibition activity in a previously established assay method [17-19]. This fluorescence-based enzymatic assay utilised Gly-Pro-7 amido-4-methylcoumarin hydrobromide (Sigma-

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Aldrich, MO, USA) as a substrate. The percent of DPP-4 inhibition was derived from the enzyme activity determined in the assay as, *100 X (1-A_t/A_0)*, where 'A_0' is the enzyme activity measured at pre-dose and 'A_t' is the activity measured post-dose at time *'t'* in the same treatment period. The percentage coefficient of variation (% CV) values for inter-and intra-assay was calculates as 4.40 and 2.20, respectively.

For the single-dose study, DPP-4 inhibition was determined at 0.00 (pre-dose), 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 hrs post-dose. For the multiple-dose study, time-points for DPP-4 inhibition were Day-1, Day-8, Day-9, Day-10 (Pre-dose) and 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, 72.00 hrs post morning dose on Day-10.

2.5 Safety Evaluations

Safety was assessed in all subjects from the screening period until the end of the study. A clinical examination including the recording of vital signs (sitting blood pressure, oral body temperature, respiratory rate and radial pulse rate) was performed at the time of screening, during the study (prior-to morning dose, 3.00, 7.00, 11.00, 15.00, 48.00, 72.00 hrs post-dose) and end of the study. Clinical blood biochemistry (SGOT, SGPT, bilirubin, creatinine, amylase, and urea), haematology and abdomen USG were performed for all participants before check-in of Period-I and end of the study. Physical medical examinations were carried out at check-in and check-out of each period. All subjects were encouraged to report any sort of discomfort experienced during the study. Throughout the study course, participants were personally questioned about their well-being.

2.6 Ethical Standards

An ethical, scientific, and medical appropriateness of the study protocols were reviewed by an independent ethics committee, "The Aurangabad committee for Ethics Registered under the Drugs Controller General of India (DCGI), Government of India, New Delhi, India". Both the studies were conducted under the ethical principles originating in the Indian Council of Medical Research (ICMR) guidelines for Biomedical Research on Human Subjects (2006), ICH (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) E6 (R2): Guideline for Good Clinical Practice (GCP) (November 2016), New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E) and the Declaration of Helsinki (Brazil, October 2013). All subjects understood and signed the informed consent form to participate in the study. The study protocols were approved and registered with DCGI as BENOC No. BE/SND/78/2019 (Single-dose study) and BE/SND/77/2019 (Multiple-dose study).

2.7 Statistical Analysis

The values for WAI (0-24 h) were calculated by dividing the AUC value for DPP-4 inhibition over 0-24 hrs by 24. During each study, PK and PD measures were analysed using WinNonlin 6.4 and SAS 9.3 software.

3. RESULTS

3.1 Single-dose study endpoints

A total of 33 from 36 enrolled subjects completed both the periods of single-dose study successfully. Two subjects failed to report at the study site for check-in of Period-II due to personal reasons hence dropout from the study. One participant experienced elevated SGPT level during the wash-out phase, thus withdrawn from the study. The average age, body weight and height of the participants were 27.4 years, 63.52 kg and 1.69 m, respectively. All other baseline demographics and clinical baseline characteristics of the study participants are summarized in **Table 1.**

Table 1. Subjects baseline demographic and clinical characteristics for single-dose study

Characteristic	Values	
	Range	Mean ± SD
Age (years)	19 - 44	27.4 ± 05.62
Weight (kg)	53.80 – 75.38	63.52 ± 06.28
Height (m)	1.58 – 1.79	01.69 ± 0.05
Body mass index (kg/m^2)	18.5 – 27.1	22.17 ± 02.51
Fasting plasma glucose (mg/dL)	79.1 – 104.9	89.78 ± 05.72
Post meal plasma glucose (mg/dL)	66.1 – 148.5	92.39 ± 16.25

Data is expressed as Mean ± SD; N=33

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Plasma drug concentration profiles of both the vildagliptin dosage regimens after single-dose administration are depicted in **Fig. 2.**

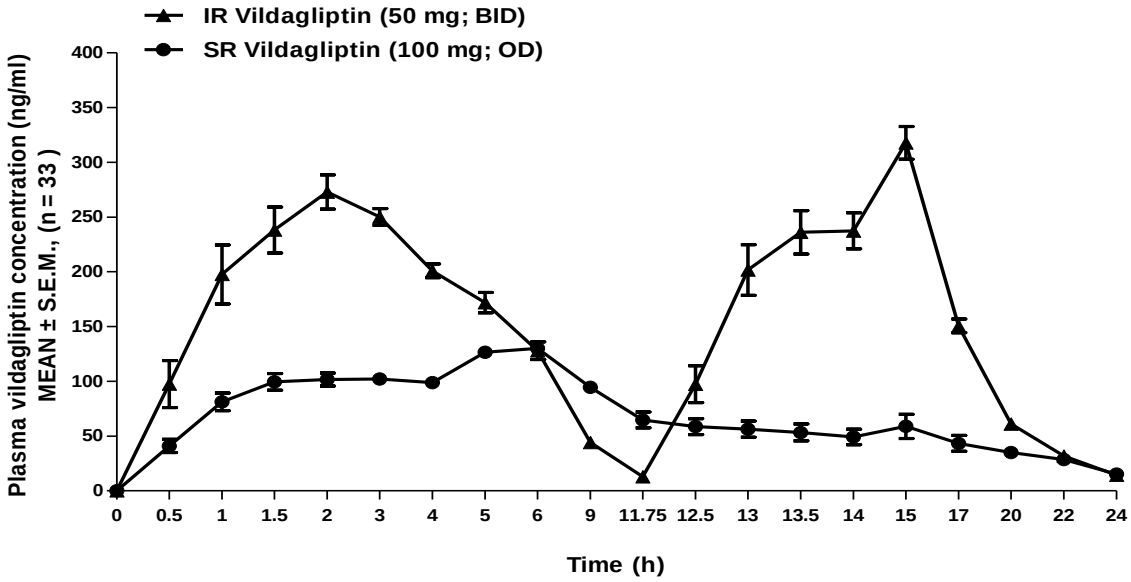

Fig. 2 Plasma concentration-time profiles of IR vildagliptin 50 mg (BID) and SR vildagliptin 100 mg (OD) tablet formulation during single-dosage study

As expected, Galvus® BID dosage resulted in a plasma drug concentration profile consisting of two peaks, each corresponding to the dose administered during morning and evening, respectively. Conversely, SR Vildagliptin tablet showed a nearly flatter and peak-less drug concentration profile over 24 hrs post-single dose. Significantly ($p<0.0001$) lesser to the Galvus® and steady level of drug exposures in SR vildagliptin treated arm [AUC_{0-24} (1645.04 ± 545.23 vs 3042.37 ± 381.22, respectively)] resulted in distinct PK characters (**Table 2)**.

Table 2. Single-dose pharmacokinetic characters of IR vildagliptin 50 mg (BID) and SR vildagliptin 100 mg (OD) tablet regimens in healthy Indian male subjects

PK Parameters		**SR vildagliptin 100 mg Tablet (OD) (N=33)**	**IR vildagliptin 50 mg Tablet (BID) (N=33)**
C_{max}(ng/mL)	**Range**	86.3-234.98	232.89-572.18
	Mean ± SD	147.7 ± 31.47 *	379.96 ± 82.59
AUC_{0-24} (ng.hr/mL)	**Range**	936.15-2957.58	2303.32-3928.72
	Mean ± SD	1645.04 ± 545.23 *	3042.37 ± 381.22
T_{max} (hours)	**Range**	1.00-15.00	0.50-15.00
	Mean ± SD	5.29 ± 3.62 *	9.06 ± 6.26
	Median	5.00	13
$t_{1/2}$ (hours)	**Range**	1.32-22.08	1.4-3.05
	Mean ± SD	4.61 ± 4.08 *	1.95 ± 0.37
	Median	3.52	1.85

*Data presented as Mean ± SD; *p<0.0001 vs IR vildagliptin 50 mg tablet by Student's paired t-test*

C_{max}, maximum plasma concentration; AUC_{0-24}, area under plasma concentration-time curve from time 0 to 24 hrs post-dose; T_{max}, time to reach C_{max}; $t_{1/2}$, terminal elimination half-life

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All PK measures are expressed as mean ± SD. The observed PK parameters of both (OD vs BID) the dosage regimens were, C_{max} (147.7 ± 31.47 vs 379.96 ± 82.59), T_{max} (5.29 ± 3.62 vs 9.06 ± 6.26), $t_{1/2}$ (4.61 ± 4.08 vs 1.95 ± 0.37). Statistically, all these PK measures are significantly ($p<0.0001$) different between groups.
As expected, the Galvus® BID regimen exhibited more than 80% DPP-4 inhibition till 24 hrs post-first dose (**Fig. 3**).

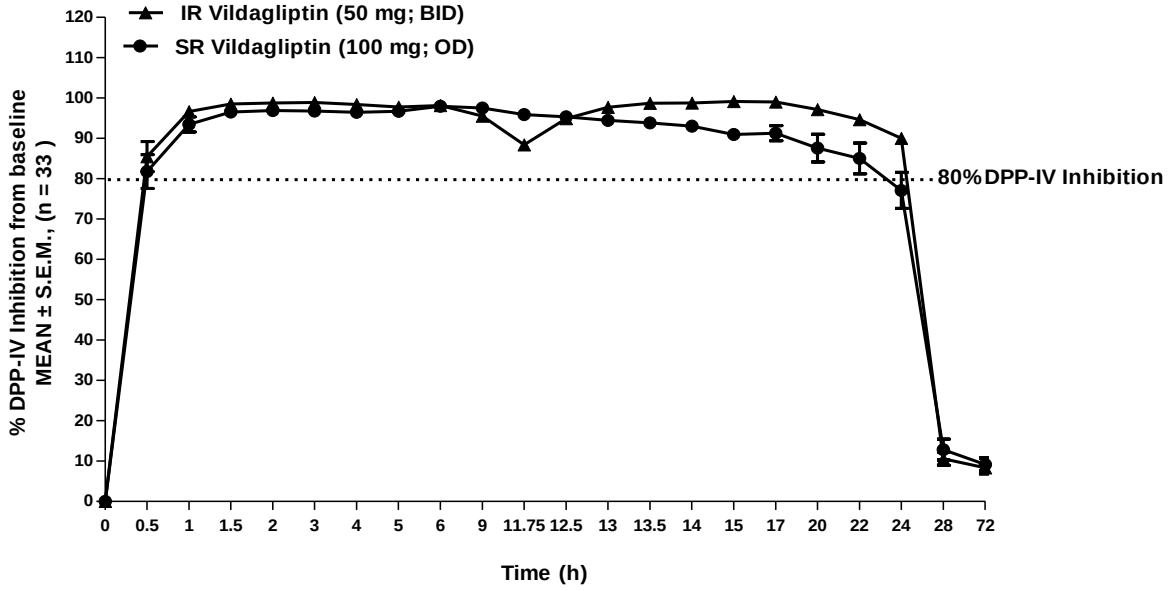

Fig. 3 Comparative DPP-4 inhibition profiles of IR vildagliptin 50 mg (BID) and SR vildagliptin 100 mg tablet (OD) after single-dosage administration

Similarly, single-dose SR vildagliptin 100 mg tablet demonstrated more than 80% DPP-4 inhibition profile for approximately 23 hrs with 77.11% inhibition at 24 hrs. Moreover, mean WAI (0-24h) values (**Fig. 4)** for both vildagliptin regimens (OD vs BID) were comparable (92% vs 95%, respectively).

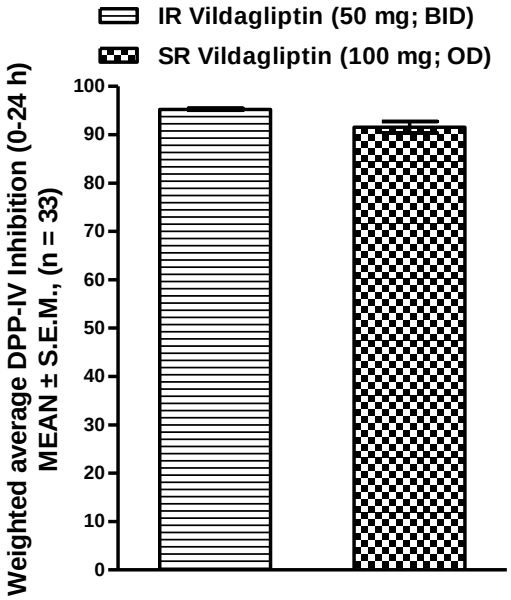

Fig. 4 Weighted average DPP-4 inhibition till 24 hrs [WAI (0-24h)] post-single dosage administration of IR vildagliptin 50 mg (BID) and SR vildagliptin 100 mg (OD) tablet

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In this single-dosage administration study, both the vildagliptin tablet formulations were found safe and well-tolerated. One mild nature adverse event was reported (increased SGPT level) during the wash-out phase which was resolved post-follow-up medications. However, the subject was withdrawn from the study.

3.2 Multiple-dose study endpoints

Out of 36 recruited subjects, 32 participants completed a two-period, multiple-dosage study. On the Day-2 of Period-I and Day-03 of Period-II, two participants expressed their wish to discontinue their further participation in the study due to personal reasons. Therefore, both the subjects were dropout from the study. Another two volunteers did not report the study facility for Period-II check-in, hence considered as a dropout from the study. Details on demographics and other baseline characteristics of the study participants are represented in **Table 3**.

Table 3. Baseline demographic and clinical characteristics of participants in multiple-dose study

Characteristic	Values	
	Range	**Mean ± SD**
Age (years)	20 - 40	27.9 ± 05.03
Weight (kg)	51.24 – 88.0	64.58 ± 10.95
Height (m)	1.58 – 1.79	01.689 ± 0.04
Body mass index (kg/m^2)	18.5 - 29.7	22.64 ± 03.50
Fasting plasma glucose (mg/dL)	76.3 – 113.8	90.75 ± 08.80
Post meal plasma glucose (mg/dL)	68.0 – 146.1	101.43 ± 17.41

Data presented as Mean ± SD; N=32

The mean age, body weight and height of participating subjects were 27.9 years, 64.5 kg and 1.68 m, respectively. All 32 subjects completing the study protocol were included in the formulation safety assessment.

Plasma concentration-time profiles on consecutive 10-days administration of Galvus® and the investigational SR vildagliptin tablet formulations are illustrated in **Fig. 5** while other calculated PK measures are summarised in **Table 4.**

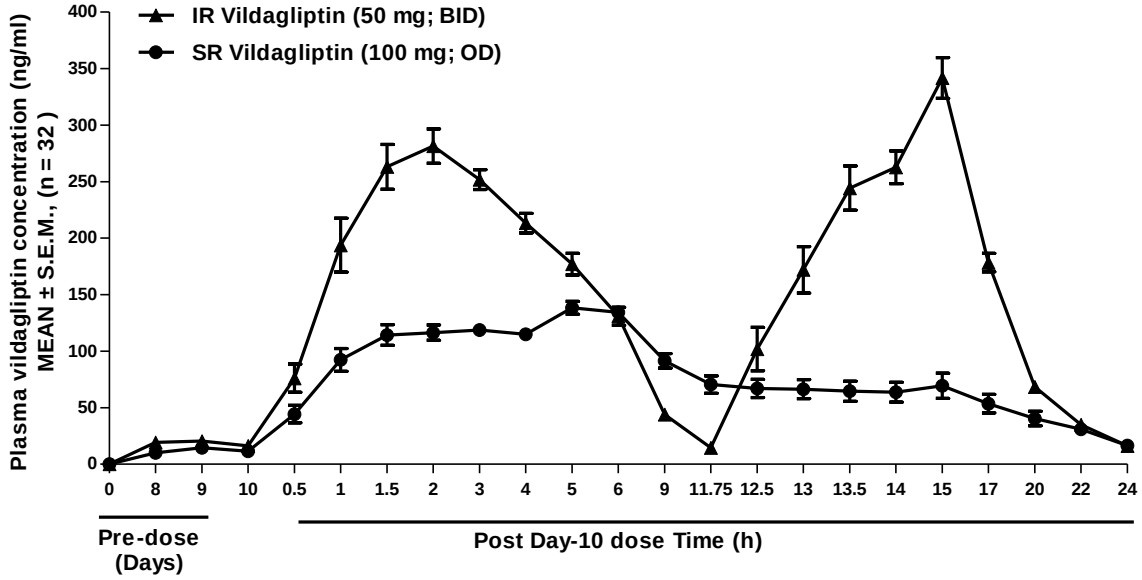

Fig. 5 Plasma vildagliptin concentrations after consecutive 10 days administration of IR vildagliptin 50 mg (BID) and SR vildagliptin 100 mg tablet (OD) regimens (multiple-dose study)

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Table 4. Pharmacokinetic measures on IR vildagliptin 50 mg (BID) and SR vildagliptin 100 mg (OD) tablet after 10-consecutive days oral dosing in healthy Indian males (N=32)

PK Parameters		SR vildagliptin 100 mg Tablet (OD)	IR vildagliptin 50 mg Tablet (BID)
C_{maxss} (ng/mL)	Range	97.05-227.13	239.86-667.22
	Mean ± SD	163.59 ± 29.34 *	388.24 ± 95.97
$AUC_{0-\tau}$ (ng.hr/mL)	Range	685.96-2997.24	2314.57-4898.89
	Mean ± SD	1815.36 ± 635.71 *	3223.27 ± 658.55
$C_{\tau ss}$(ng.hr/mL)	Range	0.00-65.07	04.92-44.13
	Mean ± SD	16.48 ± 18.26	16.32 ± 9.24
T_{maxss} (hr)	Range	0.50-15.00	1.00-15.00
	Mean ± SD	4.65 ± 3.61 #	10.53 ± 6.16
	Median	5.00	14.5
T_{halfss}(hr)	Range	1.08-9.94	1.45-2.90
	Mean ± SD	3.71 ± 2.09 $	1.92 ± 0.33
	Median	3.11	1.90

*Data presented as Mean ± SD; *p<0.0001, #p<0.0039, $p<0.0004 vs IR vildagliptin 50 mg (BID) by Student's paired t-test; C_{maxss}, the concentration maximum at steady state; AUC0-τ, the area under the curve at steady state; Cτss, the trough concentration; T_{maxss}, time to reach maximum plasma concentration at steady state; T_{halfss}, the half-life value at steady state.*

Different from the Galvus® BID dosage regimen, SR vildagliptin 100 mg tablet showed nearly a steady-state, peak-less and flatter plasma concentration profile on Day-10. This significantly (p<0.0001) reduced but extended drug exposure in SR vildagliptin 100 mg OD tablet treated arm attributed to distinct PK profile than Galvus® BID regimen [(AUC_0-τ (1815.36 ± 635.71 vs 3223.27 ± 658.55, respectively)]. The observed significant (p<0.0001) difference in PK measures included, C_{maxss} (163.59 ± 29.34 vs 388.24 ± 95.97), T_{maxss} (4.65 ± 3.61 vs 10.53 ± 6.16) and T_{halfss} (3.71 ± 2.09 and 1.92 ± 0.33), respectively. However, the steady-state trough concentrations ($C_{\tau ss}$) measured at 24 hrs post-dose on Day-10, were statistically similar in both the formulation treatment arms (16.48 ± 18.26 vs 16.32 ± 9.24, respectively), indicating the ability of SR vildagliptin 100 mg OD tablet formulation to furnish similar drug concentration to Galvus® BID regimen at 24 hrs post-dose.

Comparative DPP-4 inhibition profiles of the Galvus® (BID) and SR vildagliptin (OD) tablet formulations upon their consecutive 10-days administration is depicted in **Fig. 6**.

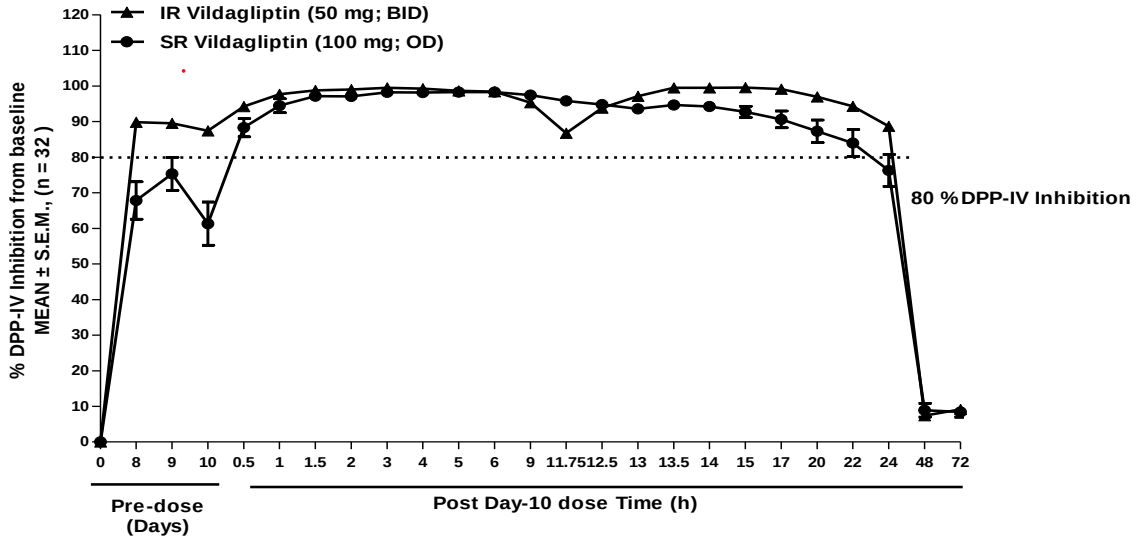

Fig. 6 DPP-4 inhibition profiles of IR vildagliptin 50 mg (BID) and SR vildagliptin 100 mg tablet (OD) regimens following consecutive 10 days oral administration

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Briefly, the Galvus® BID regimen demonstrated more than 80% DPP-4 inhibition till 24 hrs post-Day-10 dose. However, DPP-4 inhibition at 48 and 72 hrs was found to be negligible (nearly 8-9%). Comparably, investigational SR vildagliptin 100 mg tablet also exhibited more than 80% DPP-4 inhibition till nearly 23 hrs and 76.28% inhibition at 24 hrs on Day-10 post-dose. Similar to Galvus®, SR vildagliptin also showed negligible (nearly 7-8%) inhibition at 48 and 72 hrs. However, the calculated mean values for WAI (0-24h) were comparable (91.8% vs 95.3%) between the groups (SR vildagliptin vs Galvus®, respectively) (**Fig. 7)**. Both the vildagliptin dosage formulations were found to be safe and well-tolerated in this 10-days multiple-dose study. No single adverse event reported in the study in either treatment arm.

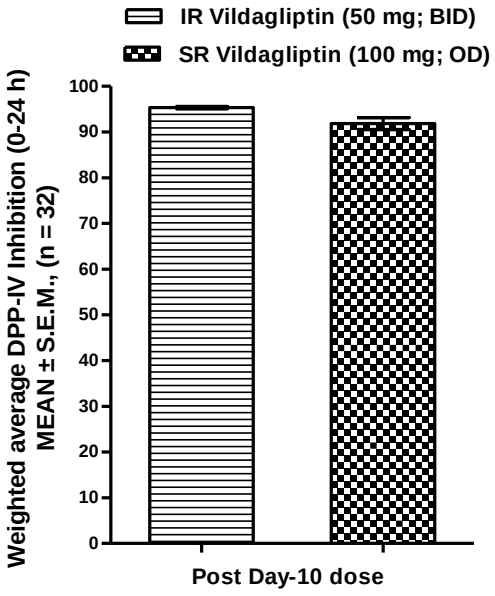

Fig. 7 Weighted average DPP-4 inhibition till 24 hrs [WAI (0-24 h)] after administration of IR vildagliptin 50 mg (BID) and SR vildagliptin 100 mg (OD) tablet formulation on Day-10

4. DISCUSSION

In this study, single and multiple-dose PK-PD performance characteristics of a newer SR vildagliptin 100 mg tablet formulation was characterized and compared with the marketed IR 50 mg BID regimen in healthy male volunteers. Classically, vildagliptin 50 mg BID therapy is prescribed for the clinical management of T2D as a monotherapy or in combination with other anti-hyperglycemic agents [11]. However, introducing OD therapy is expected to enhance the patient convenience and compliance compared with the BID regimen. Therefore, we explored OSMO laser technology to develop an SR vildagliptin tablet formulation of 100 mg strength for OD administration. Using a similar technology platform, earlier we successfully formulated a 50 mg SR vildagliptin tablet to achieve extended DPP-4 inhibition coverage in combination therapy [19].

Osmosis-mediated oral drug formulations are known to maintain sustained therapeutic levels of plasma drug concentrations for a longer interval without peak-to-trough fluctuations. These predictable uniform therapeutic plasma drug exposure result in a consistent, prolonged therapeutic effect and reduce drug-related side effects. Moreover, the drug release in this system is independent of gastric pH, hydrodynamic conditions and the presence of the food in the gastrointestinal tract. The constant pharmacological response due to controlled drug delivery avoids the normal peak and valley patterns associated with multiple dosing of conventional IR formulations [16, 20-22]. Therefore, different PK characters were expected in the current study with investigational SR vildagliptin tablet formulation than marketed IR tablet formulation, Galvus®.

In comparison with the Galvus® BID regimen, SR vildagliptin OD tablet dosage exhibited a reduction in peak plasma drug concentrations (C_{max}), overall drug exposures ($AUC_{0\text{-}24\ hr}$), and time to reach maximum plasma concentration (T_{max}) after single and multiple-dose administration. However, it increased the half-life values ($t_{1/2}$) in both studies. Collectively, these distinct PK characters confirm the sustained-release nature of investigational vildagliptin 100 mg tablet formulation. Moreover, it produced a

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longer plateau of steady drug concentrations ranging 14-130 ng/mL for 24 hrs post-dose. It may be due to the innovative formulation design of SR vildagliptin 100 mg tablet which consists of an inner pull layer, holding 85% of sustained-release active vildagliptin and an outer film coat containing 15% of the drug as an IR load.

For vildagliptin, it is reported that 4.5 nmol/L of drug concentration is obligatory to achieve 50% DPP-4 inhibition (IC_{50}) in patients with T2D. However, concentration recommended to achieve 90% DPP-4 inhibition (IC_{90}) was estimated to be 15 ng/mL [23, 24]. Therefore, in the current study, SR vildagliptin tablet formulation-induced peak-less plateau of vildagliptin concentrations ranging from 14 to 130 ng/mL was sufficient enough to elicit nearly 80% DPP-4 inhibition till 24 hrs [13].

In line with previous reports, the current study demonstrated more than 80% DPP-4 inhibition with Galvus® BID regimen till 24 hrs, corresponding to high drug exposures after single and multiple-dosage administration [11, 13, 24]. However, in case of SR vildagliptin tablet formulation, nearly half level of drug exposures were pharmacologically adequate to produce 80% DPP-4 inhibition till 23 hrs and 76-77% inhibition at 24 hrs time-points. Additionally, current study also reports reduced drug exposures and extended maximal (≥80%) DPP-4 inhibition compared to earlier findings with single bolus dose of IR 100 mg vildagliptin in healthy volunteers [13]. In the case of gliptins, the inveterate fact is that the average DPP-4 inhibition over 24 hrs must exceed approximately 70% to achieve clinically relevant glucose-lowering effects. However, maximum glucose response reported with more than 70-80% DPP-4 inhibition [24]. Also, a quantitative model of the relationship between DPP-4 inhibition and glycated haemoglobin (HbA1c) response, suggested that WAI at (0-24 h) is a useful index related to HbA1c reduction [25]. In the current study, mean WAI at 0-24 h was comparable in both the tablet formulations after single and multiple-dose administration. Therefore, we speculate that the numerical difference observed in DPP-4 inhibition during single, multiple-dose at 24 hrs time-points is less likely to impact HbA1c reducing effect of SR vildagliptin tablet formulation in the chronic setting.

Overall, comparisons of the same total daily doses in this study showed that the SR tablet formulation achieved nearly 80% DPP-4 inhibition comparable to conventionally formulated IR vildagliptin dosed BID. Additionally, both the tablet formulations achieved more than 80% WAI (0-24 h) after single and multiple-dose administration. Hence, the current study achieved its set primary objective by demonstrating a non-inferior DPP-4 inhibition profile of SR vildagliptin OD regimen over Galvus® BID regimen. However, this study is limited by the fact that it was performed in healthy male subjects thus did not elucidate the impact of SR formulation on the glycaemic outcomes by measuring GLP-1, insulin or Hb1Ac levels. A separate clinical study is needed in the T2D patient population for the assessment of the formulation on the glycaemic outcomes. However, earlier experience with gliptins suggests a clinically meaningful glycaemic control after inhibition of plasma DPP-4 activity by 80% or greater due to a 2-3 folds rise in GLP-1 levels [26]. Thus, a nearly 24 hrs 80% DPP-4 inhibitory profile of SR vildagliptin tablet is most likely to elevate the post-meal GLP-1 and insulin levels in T2D patients comparably to the conventionally used BID regimen.

5. CONCLUSION

The outcomes of the current study reveal that, at equivalent total daily doses, SR tablet formulation of 100 mg vildagliptin provides a comparable DPP-4 inhibition profile to the conventional BID regimen of the marketed IR formulation, Galvus® 50 mg. Its distinct PK characters correlate with its PD profile. Moreover, the study reports SR vildagliptin 100 mg tablet as a safe and well-tolerated formulation in healthy adult males with lesser drug exposures. This newer SR tablet formulation may enhance the patient convenience and compliance with the vildagliptin therapy compare to conventional IR formulation.

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Conflict of Interest

All authors are full-time employees of Wockhardt Limited (Mumbai, India).

Informed consent

Informed consent was obtained from all individual participants included in the study.

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