



Bioequivalence Studies of New Generic Formulations of Vildagliptin and Fixed-Drug Combination of Vildagliptin and Metformin Versus Respective Originator Products in Healthy Volunteers

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ABSTRACT

Introduction: Vildagliptin and metformin are two well-established oral antidiabetics with a complementary mechanism of action. Two new generic products, vildagliptin and its fixed-drug combination (FDC) with metformin, were tested for bioequivalence versus the approved originator reference products (Galvus® and Eucreas®).

Methods: Three randomized studies with two-treatment, two-period, two-sequence crossover design were conducted in healthy adults. One study evaluated vildagliptin 50 mg tablets as single dose under fasting conditions. Vildagliptin–metformin FDC tablet strengths of 50/850 mg and 50/1000 mg were evaluated in separate studies as single dose under fed conditions, given 30 min after a standardized high-fat, high-calorie breakfast following 10 h overnight fasting. Blood samples for analysis were collected until 24 h after dosing in each study

period. Bioequivalence between test (*T*) and reference (*R*) products required 90% confidence interval (CIs) for the geometric least square (LS) mean *T/R* ratio to be within 80–125% for the pharmacokinetic parameters, maximum plasma concentration (C_{max}), and area under the curve (AUC_{0-t}).

Results: The 90% CIs of geometric LS means of *T/R* ratio for C_{max} and AUC_{0-t} with vildagliptin tablets of 50 mg were 92.22–103.94% and 99.00–102.66%, respectively; corresponding results with FDC tablets for 50/850 mg tablets were 94.81–115.41% and 95.28–106.00% for vildagliptin and 90.87–101.18% and 90.56–100.09% for metformin; for 50/1000 mg tablets C_{max} and AUC_{0-t} were 105.56–122.30% and 98.30–107.55%, respectively, for vildagliptin and 92.14–103.73% and 94.60–101.81%, respectively, for metformin. Other parameters such as $AUC_{0-\infty}$, time to maximum concentration (T_{max}), and terminal half-life ($t_{1/2}$) were comparable between test and reference products. Adverse events (AEs), mainly vomiting, were reported without relevant difference between test and reference products in each study. AEs were generally mild and transient. No severe or serious AEs occurred.

Conclusions: The new generic drug products of vildagliptin and the FDCs of vildagliptin and metformin demonstrated bioequivalence to the approved originator products and are therefore expected to provide similar therapeutic effects.

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Key Summary Points

The new generic products, vildagliptin 50 mg tablet and vildagliptin–metformin fixed-drug combination tablets at 50/850 mg and 50/1000 mg strengths, met all standard bioequivalence criteria for key pharmacokinetic parameters to the reference products Galvus® and Eucreas® in healthy subjects.

Consequently, the new generic products are expected to provide similar clinical benefits for patients with type 2 diabetes (T2D) as the approved reference products.

The generic vildagliptin 50 mg tablet and vildagliptin–metformin fixed-drug combination tablets can be an effective alternative treatment for glycemic control in patients with T2D.

INTRODUCTION

Metformin has been in continuous clinical use within the management of type 2 diabetes (T2D) for more than 60 years [1]. T2D treatment is a chronic progressive disease requiring long-life therapy. Today treatment decisions are guided by a patient-centered approach based on cardiovascular comorbidities (established atherosclerotic cardiovascular disease; heart failure; chronic kidney disease), risk of specific side effects, and patient preferences. Metformin remains a cornerstone as initial pharmacotherapy in the management of T2D, although new drug classes such as dipeptidyl peptidase 4 (DPP4) inhibitors, sodium–glucose cotransporter 2 (SGLT2) inhibitors, and glucagon-like peptide 1 receptor agonists (GLP-1 RA) have expanded the treatment armamentarium for T2D tremendously [2–4]. The efficacy of an

antidiabetic drug tends to wane as the beta-cell dysfunction underlying T2D progresses [5]. Thus, for most patients, metformin therapy will evolve to become a metformin-based combination therapy at some point [2]. People with T2D often require multiple therapies for comorbid conditions, and polypharmacy is recognized as an important part of the overall burden of disease, which impairs patients' adherence to therapy and satisfaction with treatment [6, 7].

Fixed-drug combinations (FDCs) containing metformin with another antidiabetic drug are available to facilitate treatment without adding to the overall pill burden. FDCs reduce complexity and have been shown to improve adherence and glycemic control and increase treatment satisfaction compared to patients receiving free drug combinations [8, 9].

Vildagliptin belongs to the DPP4 inhibitors class (gliptins) and is usually recommended as a second or later treatment option in combination with metformin [10]. Both drugs have complementary mechanisms of actions. Metformin improves glycemic control by decreasing hepatic glucose production, decreasing glucose absorption, and increasing insulin-mediated glucose uptake [11, 12]. Vildagliptin is a DPP4 inhibitor acting ultimately as an islet enhancer. DPP4 inhibition slows the inactivation of the incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, thereby increasing their plasma levels and prolonging their action, which stimulates insulin secretion from pancreatic beta cells and inhibits glucagon release from pancreatic alpha cells. Ultimately, both effects lead to decreased fasting and postprandial hepatic glucose production, and thus reduced hyperglycemia [10, 13]. The addition of vildagliptin to metformin improves glycemic control by further reduction of hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) levels and increasing the HbA1c control rate [14–18]. Vildagliptin is associated with a low risk of hypoglycemia and gastrointestinal adverse events, is body weight neutral, and cardiovascular safe. It is therefore recommended as add-on therapy to metformin depending on the patients' needs [2–4, 19–23]. Treatment costs are also to be considered and therefore generic products that

are usually less expensive can be an affordable treatment alternative.

In the following we describe the pharmacokinetic phase I studies, sponsored by Alfred E. Tiefenbacher GmbH & Co KG, Hamburg, Germany, of two new generic drug products, vildagliptin and the fixed-drug combination of metformin and vildagliptin, to evaluate their bioequivalence to the respective originator product in healthy volunteers.

METHODS

Study Drugs and Study Design

The generic test products vildagliptin 50 mg tablet and the FDC of vildagliptin and metformin at tablet strengths of 50/850 mg and 50/1000 mg have been developed by Alfred E. Tiefenbacher GmbH & Co KG, Germany. The combination products comprise metformin hydrochloride.

Three comparative bioequivalence studies were conducted in healthy male volunteers. The studies were conducted by a qualified clinical research organization in India under the responsibility of AET Laboratories Pvt Ltd, India (sponsor) according to Good Clinical Practice of Helsinki and National Guidelines for Biomedical Research on Human Subjects, Good Clinical Practices for Clinical Research in India, ICH (step 5) Guidance on Good Clinical Practice, related EU guidelines. The study protocols were approved by the local ethics committee (Anveshan Independent Ethics Committee). One study, referred to as the vildagliptin study or VIL 50 mg study, evaluated the bioequivalence of the generic test product “Vildagliptin 50 mg tablet” with the commercially available originator reference product Galvus® 50 mg tablet, distributed by Novartis Europharm Ltd., London, UK. Two studies evaluated the bioequivalence of the active ingredients vildagliptin (VIL) and metformin (MET) from the vildagliptin–metformin FDC at the strength of 50/850 mg and at 50/1000 mg (studies are referred to as FDC studies or as the VIL-MET 50/850 mg study and the VIL-MET 50/1000 mg study) with the respective tablet strength of the

commercially available originator reference product Eucreas®, distributed by Novartis Pharma GmbH, Nürnberg, Germany. The studies were registered retrospectively on the clinical trials registry ClinicalTrials.gov with the following trial registration identifier numbers: NCT05329844 for the vildagliptin 50 mg study, NCT05337969 for the vildagliptin–metformin 50/850 mg study, and NCT05329857 for the vildagliptin–metformin 50/1000 mg study.

Each study was designed as a randomized, single-center, open-label, single-dose study with two-treatment and two-period crossover design. The vildagliptin study was conducted under fasting conditions with a 7-day washout period between the two periods to minimize carryover effects and to eliminate the drug from the body. Subjects were required to take a single oral dose of either the test or reference product after a supervised overnight fasting for at least 10 h. The studies with vildagliptin–metformin FDC tablets were conducted under fed conditions (labelled administration) with a washout period of 9 days between each dosing period. The FDC of the generic test or originator reference product was taken after a supervised overnight fasting for at least 10 h and exactly 30 min after the start of a standardized high-fat high-calorie (800–1000 kcal) breakfast. The following conditions applied to all three studies: the test or reference tablet was to be swallowed as whole with 240 mL of 20% dextrose water at ambient temperature in sitting position; subjects received a standard meal at about 4.00, 9.00, and 13.00 h after dosing in each period; meal plans were identical for all periods and drinking water was not allowed from 1 h before dosing until 1 h post-dose (except for the aforementioned tablet intake), then 60 mL of the 20% dextrose water was administered every 15 min for up to 4 h after dosing; thereafter drinking water was allowed at any time. Subject allocation to treatments including the order of reference and test product in the two periods was carried out using randomization statistical techniques SAS® software (SAS® Institute Inc., USA, version 9.2). Randomization was done in block size of 2 using PROC PLAN for a balanced design.

Subjects

Subject eligibility criteria were basically the same in all three studies: healthy male volunteers, written informed consent to participate, aged between 18 and 45 (both inclusive) years, a body mass index (BMI) between 18.5 and 30 kg/m², and a minimum body weight of 50 kg. Subjects' health status was assessed on the basis of medical history, vital and clinical examination, clinical laboratory tests (hematology, blood biochemistry, urinalysis in the normal range), immunology (hepatitis B surface antigen, hepatitis C virus, human immunodeficiency virus), clinically acceptable chest X-ray and 12-lead electrocardiogram recordings during screening. Urine screening for drug abuse, alcohol breath tests, and clinical examinations were performed at the time of admission in each study period. All subjects were enrolled strictly on the basis of inclusion and exclusion criteria of the approved protocol for each study.

Blood Sampling and Handling

Blood samples (3.0 or 4.0 mL) were drawn before dosing and up to 24.00 h after each dosing period. Pre-dose blood samples were collected within 1 h prior to dosing. In each study post dose samples were drawn at 0.50, 1.00, 1.50, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, and at 24.00 h following drug administration at each period. Additional post dose time points in the vildagliptin study were at 0.25, 0.75, 1.16, 1.33, 1.67, and 1.83 h and in the FDC studies at 1.25, 1.75, 2.75, 3.25, 4.50, and 5.50 h. The applied sampling schedule allowed an adequate estimate of C_{\max} and to cover the plasma concentration–time curve long enough for a reliable estimate of the extent of absorption. Collected blood samples were centrifuged at 4000 rpm at 4 °C for 10 min and aliquots were stored at -78 ± 8 °C until analysis. Plasma concentrations of vildagliptin and metformin were measured using validated bioanalytical methods (HP)LC–ESI–MS/MS validated by the bioanalytical laboratory of Veeda Clinical Research Pvt., Ltd. for the quantification of vildagliptin and

metformin. The calibration curve for vildagliptin ranged from 2.00 to 800 ng/mL with a lower limit of quantification (LLOQ) of 2.00 ng/mL and for metformin it extends over the range from 10.0 to 4000 ng/mL with a LLOQ of 10.0 ng/mL.

Pharmacokinetic and Statistical Analyses and Sample Size Considerations

The primary pharmacokinetic (PK) parameters for assessment of bioequivalence were maximal plasma concentration (C_{\max}) and area under the concentration curve from time 0 to the last time point of measurable concentration (AUC_{0-t}). Sample sizes were determined on the basis of literature estimates, assuming a test to reference ratio of 90–111% and an intra-subject variability of approximately 26.70% for the VIL 50 mg study and of approximately 20% for the FDC studies. A total of 66 subjects were required for the VIL 50 mg study to conclude bioequivalence with approximately 80% power and 50 subjects were sufficient to prove bioequivalence with approximately 90% between the two formulations in the FDC studies. The test and reference formulations were considered bioequivalent if the geometric least square mean ratio for C_{\max} and AUC_{0-t} and its 90% confidence interval were within the bioequivalence acceptance range of 80.00–125.00%, in line with European guidelines [24].

Secondary pharmacokinetic parameters calculated were AUC extrapolated to infinite time ($AUC_{0-\infty}$), time to reach maximal plasma concentration (T_{\max}), terminal elimination half-life ($t_{1/2}$), Kel (elimination rate constant), ratio of $AUC_{0-t}/AUC_{0-\infty}$, and percentage of $AUC_{0-\infty}$ extrapolation from t last to infinity ($AUC\%_{\text{Extrap_obs}}$).

All PK parameters were calculated on the basis of non-compartmental methods using WinNonlin® Enterprise Software Version 5.3 (Pharsight Corporation, USA). The statistical comparison of ln-transformed C_{\max} and AUC_{0-t} was carried out with SAS® Version 9.2 (SAS Institute Inc., USA). Analysis of variance was performed using SAS® Version 9.2 (SAS Institute Inc., USA) for ln-transformed C_{\max} and

AUC_{0-t} using PROC GLM. The ANOVA model included treatment, period, sequence and subjects nested within sequence effects. Subject nested into the sequence would be used as the error term for checking the significance of the sequence. The sequence effect was tested at the 0.10 level of significance and all other main effects at the 0.05 level of significance. Two-sided 90% confidence intervals for the geometric least square mean ratio (T/R) obtained from the analysis of ln-transformed parameters C_{max} and AUC_{0-t} was constructed using root mean square error computed by PROC GLM. Intra-subject variability and power were calculated and reported for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} using root mean square error computed by PROC GLM.

Safety Assessments

Safety and tolerability assessments included vital signs, clinical examinations, monitoring for signs and symptoms of hypoglycemia, and hematologic and biochemistry laboratory parameters. Vital signs (sitting blood pressure and radial pulse rate) were measured before dosing (in the morning of the day of dosing) and at 1, 2, 3, 6, and 13 h after dosing in each period. Clinical examination (vital signs, physical examination) was done at the time of admission, at any time during the study conduct in case of an adverse event, and before discharge from each period. Subjects were monitored for signs and symptoms of symptomatic hypoglycemia. Blood glucose levels were determined using last drop of blood by glucometer in each study pre-dose and at defined time points post dose up to 8 h in the vildagliptin study and up to 10 h in the FDC studies. Dextrose was administered if blood glucose levels dropped below 60 mg/dL. Subjects were questioned for well-being at the time of clinical examination, during recording of vital signs, and at the time of last blood sample collection. Post-study safety assessment after collecting the last blood sample of period 2 included hematology and biochemical parameters (serum glutamic oxaloacetic transaminase, serum glutamic pyruvate transaminase,

bilirubin, creatinine, and urea). Descriptive statistics were used for safety data.

RESULTS

Demographic Characteristics

Vildagliptin 50 mg Study

Sixty-six healthy male subjects were enrolled as planned with a mean age of 29.8 years and a mean BMI of 22.89 kg/m² (Table 1 including details by study populations). Sixty-one of them completed both study periods according to protocol and were therefore included in the pharmacokinetic statistical analyses. Five subjects were excluded from PK analysis for the following reasons: vomiting episode (two subjects), positive alcohol test, withdrawal of

Table 1 Vildagliptin 50 mg study: demographic profile

	VIL 50 mg study ^a	
	Enrolled, N = 66	PK-analysis set, N = 61
Age, years ^a		
Mean ± SD	29.8 ± 6.3	30.1 ± 6.4
Range	19–44	19–44
Weight, kg		
Mean ± SD	64.1 ± 10.2	63.9 ± 9.7
Range	50.9–90.5	50.9–90.5
BMI, kg/m ²		
Mean ± SD	22.89 ± 3.24	22.81 ± 3.10
Range	18.96–29.68	18.96–29.68
Height, cm		
Mean ± SD	167.3 ± 5.5	167.4 ± 5.5
Range	154–178	154–178

PK-analysis set includes all subjects who completed both study periods

BMI body mass index, PK pharmacokinetic, SD standard deviation, VIL vildagliptin

^aAll subjects were male

Table 2 Vildagliptin–metformin FDC studies: demographic data for all enrolled subjects and PK-analysis set

	VIL-MET 50/850 mg study		VIL-MET 50/1000 mg study	
	Enrolled, <i>N</i> = 60	PK-analysis set, <i>N</i> = 49	Enrolled, <i>N</i> = 60	PK-analysis set, <i>N</i> = 48
Age, years ^a				
Mean ± SD	30.1 ± 6.1	30.3 ± 6.4	30.2 ± 6.9	30.8 ± 6.9
Range	19–44	44–19	18–44	18–44
Weight, kg				
Mean ± SD	58.7 ± 6.9	59.8 ± 6.7	62.0 ± 9.0	62.1 ± 9.5
Range	50.1–75.8	50.1–75.8	50.6–90.2	50.6–90.2
BMI, kg/m ²				
Mean ± SD	21.50 ± 2.33	21.78 ± 2.41	22.01 ± 2.81	22.17 ± 2.88
Range	18.91–27.53	18.95–18.91	18.95–29.29	19.01–29.29
Height, cm				
Mean ± SD	165.3 ± 6.1	165.8 ± 5.8	167.7 ± 5.1	167.2 ± 4.6
Range	152–186	152–186	154–179	154–176

PK-analysis set includes all subjects who completed both study periods

BMI body mass index, *FDC* fixed-drug combination, *MET* metformin, *PK* pharmacokinetic, *SD* standard deviation, *VIL* vildagliptin

^aAll subjects were male

Table 3 VIL 50 mg study: analysis of bioequivalence for vildagliptin administered under fasting conditions as single dose of a 50 mg tablet of the generic test and the originator reference product

	Geometric LS mean, <i>N</i> = 61				
	Test product (<i>T</i>)	Reference product (<i>R</i>)	<i>T/R</i> ratio (%)	<i>ISCV</i> (%)	90% <i>CI</i>
<i>C</i> _{max} (ng/mL)	219.61	224.31	97.91	19.90	92.22–103.94
<i>AUC</i> _{0–t} (h*ng/mL)	1145.79	1136.54	100.81	5.98	99.00–102.66

Test product, vildagliptin 50 mg tablet; reference product, Galvus® 50 mg

*AUC*_{0–t} area under the curve from time zero to last time point of measurable concentration, *C*_{max} maximum plasma concentration, *CI* confidence interval, *ISCV* intra-subject coefficient of variance, *LS* least square

consent, and non-compliance, i.e., failure to show up at the study facility (one subject each).

Vildagliptin–Metformin 50/850 mg Study

Sixty healthy male subjects were enrolled as planned with a mean age of 30.1 years and a mean BMI of 21.50 kg/m² (Table 2 including

details by study population). Statistical PK analysis was conducted in 49 subjects, who completed both study periods. The reasons for excluding 11 subjects were vomiting episode (six subjects), non-compliance with breakfast and not showing up at the study site (two subjects each), and drug abuse (one subject).

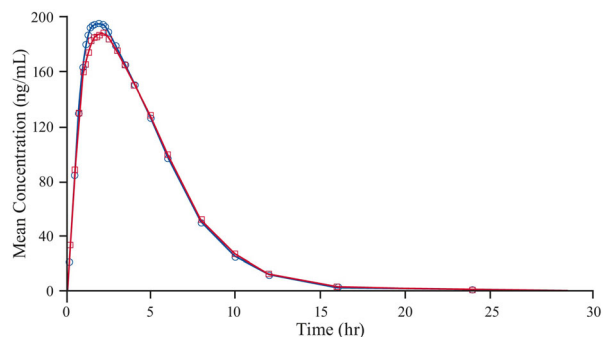


Fig. 1 Mean plasma concentration–time graph for vildagliptin after single dose of a 50 mg tablet of the generic test product (open squares) and the originator reference product (open circles) under fasted conditions. Test product, vildagliptin 50 mg tablet; reference product, Galvus® 50 mg

Vildagliptin–Metformin 50/1000 mg Study

Sixty healthy male subjects were enrolled as planned with a mean age of 30.2 years and a mean BMI of 22.01 kg/m² (Table 2 including

details by study population). Plasma samples of 48 subjects, who completed both study periods, were used for statistical PK analysis. The reason for excluding 12 subjects was an episode of vomiting.

Pharmacokinetic Parameters and Bioequivalence

Vildagliptin 50 mg Study

Analysis of bioequivalence (primary endpoint) between vildagliptin 50 mg tablets of the generic test and originator reference product showed geometric mean ratios close to 100% for the primary target parameter, i.e., 97.91% for C_{max} and 100.81% for AUC_{0–t} with 90% confidence intervals between 80% and 125% (Table 3).

The mean plasma concentration–time curves of vildagliptin over time are similar for the 50 mg tablet of the generic test product and the originator reference product (Fig. 1). Average

Table 4 VIL 50 mg study: pharmacokinetic parameters of vildagliptin administered under fasting conditions as single dose of a 50 mg tablet of the generic test and the originator reference product

	Arithmetic mean ± SD (%CV), N = 61	
	Test product	Reference product
Vildagliptin		
C _{max} , ng/mL	233.89 ± 95.94 (41.02)	234.28 ± 74.86 (31.95)
T _{max} , h ^a	2.0 [0.25–5.0]	1.8 [0.5–6.0]
AUC _{0–t} , ng*h/mL	1164.15 ± 206.47 (17.74)	1152.02 ± 192.22 (16.69)
AUC _{0–∞} , ng*h/mL	1176.54 ± 206.92 (17.59)	1163.84 ± 192.79 (16.57)
t _{1/2} , h	1.94 ± 0.58 (29.91)	1.79 ± 0.3054 (17.03)
Kel, 1/h	0.3763 ± 0.06762 (17.97)	0.3953 ± 0.05602 (14.17)
AUC _{0–t} /AUC _{0–∞} , %	98.9 ± 0.6 (0.60)	99.0 ± 0.5 (0.46)
AUC_%Extrap_obs	1.08 ± 0.59 (54.61)	1.04 ± 0.46 (44.11)

Test product, vildagliptin 50 mg tablet; reference product, Galvus® 50 mg

AUC_{0–t} area under the curve from time zero to last time point of measurable concentration, AUC_{0–∞} area under the curve from time zero to infinity, C_{max} maximum plasma concentration, CV covariance, CV intra-subject coefficient of variance, Kel elimination rate constant, SD standard deviation, t_{1/2} elimination or terminal half-life, T_{max} time to maximum concentration

^aFor T_{max}: median [range]

Table 5 VIL-MET 50/850 mg study: analysis of bioequivalence for vildagliptin and metformin administered under fed conditions as single dose of a 50/850 mg FDC tablet of the generic test and the originator reference product

	Geometric LS mean, <i>N</i> = 49				
	Test product (<i>T</i>)	Reference product (<i>R</i>)	<i>T/R</i> ratio	ISCV	90% CI
Vildagliptin					
<i>C</i> _{max} , ng/mL	129.37	123.70	104.60%	29.62%	94.81–115.41
<i>AUC</i> _{0–<i>t</i>} , ng*h/mL	770.04	766.24	100.50%	15.82%	95.28–106.00
Metformin					
<i>C</i> _{max} , ng/mL	1249.90	1303.52	95.89%	15.95%	90.87–101.18
<i>AUC</i> _{0–<i>t</i>} , ng*h/mL	12,681.00	13,319.50	95.21%	14.85%	90.56–100.09

Test product, vildagliptin–metformin 50/850 mg tablet; reference product, Eucreas® 50/850 mg
*AUC*_{0–*t*} area under the curve from time zero to last time point of measurable concentration, *CI* confidence interval, *C*_{max} maximum plasma concentration, *FDC* fixed-drug combination, *ISCV* intra-subject coefficient of variance, *LS* least squares, *MET* metformin, *VIL* vildagliptin

Table 6 VIL-MET 50/1000 mg study: analysis of bioequivalence for metformin and vildagliptin administered under fed conditions as single dose of a 50/1000 mg FDC tablet of the generic test and the originator reference product administered under fed conditions

	Geometric LS mean, <i>N</i> = 48				
	Test product (<i>T</i>)	Reference product (<i>R</i>)	<i>T/R</i> ratio	ISCV	90% CI
Vildagliptin					
<i>C</i> _{max} , ng/mL	142.08	125.05	113.62%	21.72%	105.56–122.30
<i>AUC</i> _{0–<i>t</i>} , ng*h/mL	844.12	820.97	102.82%	13.16%	98.30–107.55
Metformin					
<i>C</i> _{max} , ng/mL	1407.75	1439.99	97.76%	17.41%	92.14–103.73
<i>AUC</i> _{0–<i>t</i>} , ng*h/mL	14,211.42	14,480.34	98.14%	10.74%	94.60–101.81

Test product, generic vildagliptin–metformin 50/1000 mg tablet; reference product, Eucreas® 50/1000 mg
*AUC*_{0–*t*} area under the curve from time zero to last time point of measurable concentration, *CI* confidence interval, *C*_{max} maximum plasma concentration, *FDC* fixed-drug combination, *ISCV* intra-subject coefficient of variance, *LS* least squares

values of secondary pharmacokinetic parameters of vildagliptin were comparable between both formulations (Table 4).

Vildagliptin–Metformin FDC Studies

Statistical analysis of bioequivalence between the FDCs of the generic test product vildagliptin–metformin 50/850 mg tablet and

the corresponding originator reference product for the 50/850 mg tablet strength showed geometric mean ratios of the primary PK parameters around 95% for metformin and between 100% and 104% for vildagliptin with 90% confidence intervals between 80% and 125% (Table 5). For the 50/1000 mg tablets geometric mean ratios of the primary PK parameter for

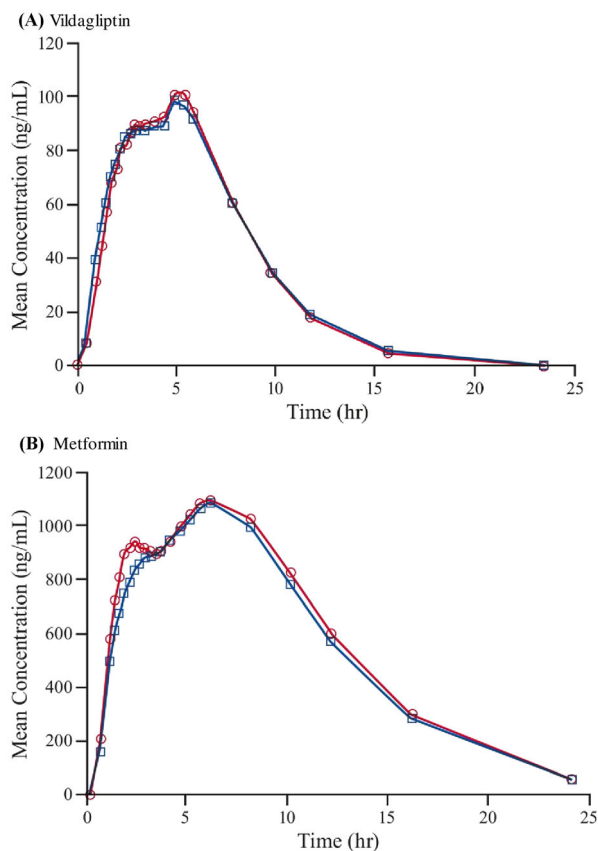


Fig. 2 Mean plasma concentration–time graphs for vildagliptin (a) and for metformin (b) after single dose of a 50/850 mg FDC tablet of generic test product (open squares) and originator reference product (open circles) under fed conditions. Test product, vildagliptin–metformin 50/850 mg tablet; reference product, Eucreas® 50/850 mg

metformin were around 98% and between 102% and 114% for vildagliptin with 90% confidence intervals always in the required range of 80% and 125% (Table 6).

The curves for mean plasma concentrations over time for the vildagliptin and metformin component from the generic test products and originator reference FDC products overlapped closely for both tablet strengths of 50/850 mg (Fig. 2) and 50/1000 mg (Fig. 3).

The average values of secondary PK parameters were comparable between the formulations for both analytes, vildagliptin and metformin, of each tablet strength, i.e., 50/850 mg (Table 7) and 50/1000 mg (Table 8).

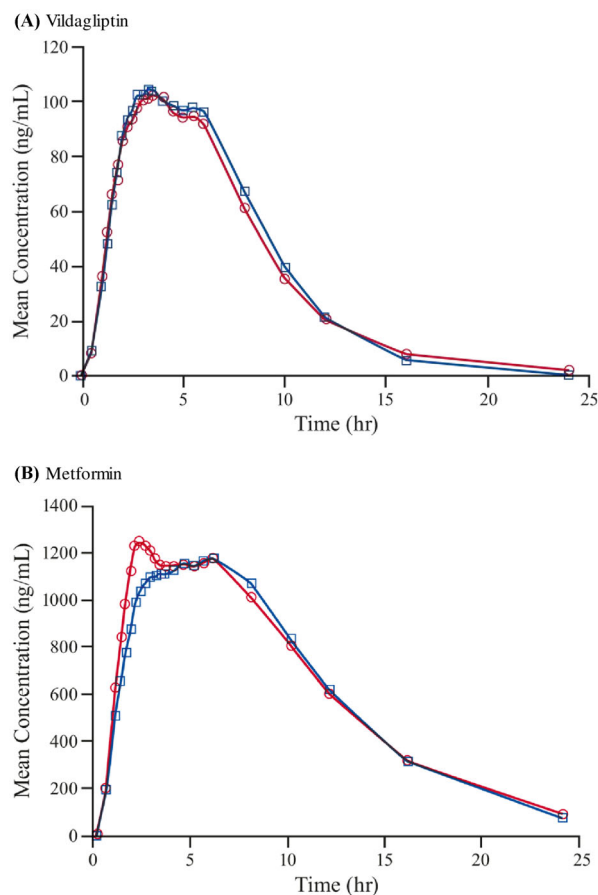


Fig. 3 Mean plasma concentration–time graphs for vildagliptin (a) and for metformin (b) after single dose of a 50/1000 mg FDC tablet of generic test product (open squares) and originator reference product (open circles) administered under fed conditions. Test product, vildagliptin–metformin 50/1000 mg tablet; reference product, Eucreas® 50/1000 mg

Safety and Tolerability

Vildagliptin 50 mg Study

No serious AE was reported. Four (6.1%) of 66 dosed subjects reported a non-serious AE during the study, i.e., single mild vomiting episode in three subjects (possibly related to test drug in two subjects and to reference drug in one subject) and decreased blood glucose level of mild intensity in two subjects (possibly related to test drug). All AEs were transient and resolved. Decreased blood glucose level required treatment with dextrose as per protocol.

Table 7 VIL-MET 50/850 mg study: pharmacokinetic parameters of metformin administered under fed conditions as single dose of a 50/850 mg FDC tablet of the generic test and the originator reference product

	Arithmetic mean \pm SD (%CV), $N = 49$		p value
	Test product	Reference product	Test vs reference
Vildagliptin			
C_{max} , ng/mL	140.65 \pm 55.75 (39.64)	130.08 \pm 40.78 (31.35)	0.136
T_{max} , h ^a	5.0 [1.25–12.0]	4.5 [1.25–10.0]	–
AUC_{0-t} , ng*h/mL	792.11 \pm 180.30 (22.76)	784.49 \pm 175.24 (22.34)	0.238
$AUC_{0-\infty}$, ng*h/mL	809.86 \pm 182.26 (22.50)	801.39 \pm 178.42 (22.26)	0.251
$t_{1/2}$, h	2.12 \pm 0.59 (27.70)	2.04 \pm 0.35 (17.39)	0.670
Kel , 1/h	0.3456 \pm 0.07415 (21.46)	0.3497 \pm 0.06026 (17.23)	0.613
$AUC_{0-t}/AUC_{0-\infty}$, %	97.75 \pm 2.13 (2.18)	97.86 \pm 1.20 (1.23)	0.495
$AUC_{\%Extrap_obs}$	2.25 \pm 2.13 (94.77)	2.14 \pm 1.20 (56.30)	0.492
Metformin			
C_{max} , ng/mL	1287.89 \pm 327.53 (25.43)	1356.76 \pm 411.27 (30.31)	0.590
T_{max} , h ^a	5.5 [1.0–10.0]	5.5 [1.0–10.0]	–
AUC_{0-t} , ng*h/mL	13,060.37 \pm 3146.60 (24.09)	13,629.10 \pm 3007.09 (22.06)	0.238
$AUC_{0-\infty}$, ng*h/mL	13,454.16 \pm 3207.56 (23.84)	14,035.55 \pm 3106.23 (22.13)	0.215
$t_{1/2}$, h	3.90 \pm 0.88 (22.50)	3.83 \pm 0.46 (12.08)	0.670
Kel , 1/h	0.1829 \pm 0.02566 (14.03)	0.1834 \pm 0.02037 (11.10)	0.669
$AUC_{0-t}/AUC_{0-\infty}$, %	96.97 \pm 2.69 (2.78)	97.15 \pm 1.67 (1.71)	0.495
$AUC_{\%Extrap_obs}$	3.03 \pm 2.69 (88.89)	2.85 \pm 1.67 (58.42)	0.492

Test product, vildagliptin–metformin 50/850 mg tablet; reference product, Eucreas® 50/850 mg
 AUC_{0-t} area under the curve from time zero to last time point of measurable concentration, $AUC_{0-\infty}$ area under the curve from time zero to infinity, CI confidence interval, C_{max} maximum plasma concentration, CV covariance, FDC fixed-drug combination, $ISCV$ intra-subject coefficient of variance, Kel elimination rate constant, SD standard deviation, $t_{1/2}$ elimination or terminal half-life, T_{max} time to maximum concentration

^aFor T_{max} : median [range]

Vildagliptin–Metformin 50/850 mg Study

No serious AE was reported. Nine (13.6%) of 60 dosed subjects reported a non-serious AE during the study, i.e., single mild vomiting episode in seven subjects considered possibly related to study drug in five subjects (three with test drug and two with reference drug) and not related to test or reference drug (one subject each); mild dizziness in one subject (possibly related to test drug) and moderate accidental injury in one subject (not related to test drug). All AEs were

transient, not associated with other complaints, and resolved.

Vildagliptin–Metformin 50/1000 mg Study

No serious AE was reported. Twelve (20.0%) of 60 dosed subjects reported a non-serious AE during the study, i.e., vomiting in all cases. Vomiting occurred as a single episode of mild intensity in 11 subjects, and each was considered possibly related to study drug (eight subjects during test drug period and three subjects

Table 8 VIL-MET 50/1000 mg study: pharmacokinetic parameters of metformin and vildagliptin after fed administration of a single dose of a 50/1000 mg FDC tablet of the generic test and the originator reference product

	Arithmetic mean \pm SD (%CV), $N = 48$		p value
	Test product	Reference product	Test vs reference
Vildagliptin			
C_{max} , ng/mL	149.53 \pm 50.14 (33.53)	131.85 \pm 44.08 (33.43)	0.004
T_{max} , h ^a	3.8 [1.5–8.0]	4.0 [1.5–12.0]	–
AUC_{0-t} , ng*h/mL	858.27 \pm 159.92 (18.63)	844.25 \pm 218.62 (25.89)	0.296
$AUC_{0-\infty}$, ng*h/mL	878.74 \pm 160.08 (18.22)	1404.58 \pm 3905.91 (278.08) ^b	0.019 ^b
$t_{1/2}$, h	2.17 \pm 0.55 (25.19)	6.46 \pm 29.06 (449.78) ^b	0.063 ^b
K_{el} , 1/h	0.3333 \pm 0.06001 (18.01)	0.3157 \pm 0.08026 (25.42) ^b	0.056 ^b
$AUC_{0-t}/AUC_{0-\infty}$, %	97.66 \pm 2.54 (2.59)	95.87 \pm 13.29 (13.87)	0.972
$AUC_{\%Extrap_obs}$	2.35 \pm 2.54 (108.05)	4.13 \pm 13.29 (322.17)	0.972
Metformin			
C_{max} , ng/mL	1465.06 \pm 414.93 (28.32)	1487.61 \pm 391.28 (26.30)	0.491
T_{max} , h ^a	4.75 [1.75 – 10.00]	3.50 [1.25–8.00]	–
AUC_{0-t} , ng*h/mL	14,507.08 \pm 2837.47 (19.56)	14,788.36 \pm 2951.15 (19.96)	0.296
$AUC_{0-\infty}$, ng*h/mL	14,929.91 \pm 2979.30 (19.96)	16,233.59 \pm 8270.26 (50.95)	0.335
$t_{1/2}$, h	3.87 \pm 0.60 (15.44)	4.62 \pm 4.64 (100.43)	0.747
K_{el} , 1/h	0.1827 \pm 0.02389 (13.08)	0.1793 \pm 0.03598 (20.07)	0.734
$AUC_{0-t}/AUC_{0-\infty}$, %	97.24 \pm 1.40 (1.44)	95.62 \pm 10.03 (10.49)	0.303
$AUC_{\%Extrap_obs}$	2.76 \pm 1.40 (50.81)	4.38 \pm 10.03 (229.06)	0.303

Test product, vildagliptin–metformin 50/1000 mg tablet; reference product, Eucreas® 50/1000 mg
 AUC_{0-t} area under the curve from time zero to last time point of measurable concentration, $AUC_{0-\infty}$ area under the curve from time zero to infinity, CI confidence interval, C_{max} maximum plasma concentration, CV covariance, FDC fixed-drug combination, $ISCV$ intra-subject coefficient of variance, K_{el} elimination rate constant, SD standard deviation, $t_{1/2}$ elimination or terminal half-life, T_{max} time to maximum concentration

^aFor T_{max} : median [range]

^bIncluding a subject with $AUC_{extrapolated}$ 93.4% of $AUC_{0-\infty}$

during reference drug period). One subject experienced two vomiting episodes, both of moderate intensity and considered not related to study drug (reference drug period). All AEs were transient, not associated with other complaints, and resolved.

DISCUSSION

The new generic film-coated tablet formulation of vildagliptin 50 mg and the combination of vildagliptin and metformin tablets (50/850 mg and 50/1000 mg) proved to be bioequivalent to the same tablet strength of the respective approved originator reference products Galvus® (Novartis Europharm Ltd, UK) and Eucreas®

(Novartis Pharma GmbH, Germany). Each of the three PK studies was powered adequately for bioequivalence testing between the formulations. The dropout rate was slightly higher in the two FDC studies than anticipated, i.e., 11 subjects (VIL-MET 50/850 mg study) and 12 subjects (VIL-MET 50/1000 mg study) instead of the anticipated 10 subjects per study. The standard bioequivalence criteria for rate and extent of absorption of the active ingredients vildagliptin and metformin were met in each of the three studies. Bioequivalence was judged on the basis of the 90% confidence intervals for both analytes, vildagliptin and metformin, which were well in the pre-set acceptance range of 80–125% for the primary PK parameter C_{max} and AUC_{0-t} [24]. The safety and tolerability are well established for the new generic formulations. No serious adverse events were reported in these studies. The proven bioequivalence data allow one to extrapolate the clinical evidence on efficacy and safety from the originator reference products to the new generics.

The pharmacokinetics of vildagliptin and metformin are not relevantly influenced by age, gender, or BMI and therefore the subject selection for the presented studies was reasonable. The administration conditions applied in the three studies are in line with the general guidance for bioequivalence studies and the recommended administration in the product information. For vildagliptin it is known that food slightly delays the time to peak plasma concentrations but does not alter overall exposure which allows vildagliptin to be taken irrespective of a meal. Because of this and in line with the European Medicines Agency (EMA) guidance vildagliptin was tested in the present study in the fasted state, which is the most sensitive condition to detect potential differences between formulations. The FDC vildagliptin-metformin has to be administered with a meal because of its metformin component and was therefore tested under fed conditions in a two-way crossover design [13, 24, 25].

Overall, the generic test products vildagliptin and the vildagliptin-metformin FDC were well tolerated. The AEs reported for the generic test and originator reference formulations were generally mild and transient. Vomiting was the

most commonly reported AE and more frequently reported after administration of the metformin containing FDC tablets, however without relevant difference between the test and reference formulation.

Vildagliptin is intended to be used as an adjunct to diet and exercise to improve glycemic control in patients with T2D, either as monotherapy if metformin is inappropriate because of contraindication or intolerance or in combination with other antidiabetics if these do not provide adequate glycemic control. Combination includes add-on therapy to metformin, a sulfonylurea (SU) or a thiazolidinedione, or vildagliptin combined with metformin and a SU or with insulin \pm metformin [13, 25]. The new generic formulations for the mono component vildagliptin and the FDC of vildagliptin and metformin are expected to provide similar therapeutic efficacy and safety to the respective reference products on the basis of their bioequivalence. Vildagliptin-metformin FDC allows one to ease the treatment in the same settings by substituting the mono components with the FDC and thereby reduce tablet intake and complexity of treatment. A significantly higher treatment adherence was achieved in a non-interventional study in patients with T2D taking the FDC of vildagliptin and metformin versus the free-drug combination [26].

Limitations

There may be some possible limitations in this study. The findings of this study have to be seen in the light of comparison of pharmacokinetic behavior, safety, and tolerability of test and reference product.

CONCLUSIONS

The generic formulation of vildagliptin 50 mg tablet and the FDC tablets of vildagliptin and metformin at two strengths, 50/850 mg and 50/1000 mg, are bioequivalent to the respective originator reference products at the same tablet strengths. Therefore, the new generic products are expected to behave similarly in vivo and

provide similar therapeutic effects and tolerability as the reference products and can therefore substitute the reference products in the appropriate indications.

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Disclosures. Yvonne Schnaars, Sumedh Gaikwad, and Ulrike Gottwald-Hostalek are employees of the Merck Healthcare KGaA, Darmstadt, Germany which holds the marketing authorization of the generic products evaluated in the bioequivalence studies. Ulrike Klingberg is an employee of Alfred E. Tiefenbacher GmbH & Co KG, Hamburg, Germany which developed the generic products. Hari Kiran Chary Vadla and Vamshi Ramana Prathap are employees of AET Laboratories Private

Limited, Hyderabad, India which sponsored the bioequivalence studies of the generic products.

Compliance with Ethics Guidelines. The study protocols were approved by the local ethics committee "Anveshan Independent Ethics Committee". All study procedures were performed in accordance with the 1964 Helsinki declaration and its later amendments and National Guidelines for Biomedical Research on Human Subjects, Good Clinical Practices for Clinical Research in India, ICH (step 5) Guidance on Good Clinical Practice, and related EU guidelines. Informed consent was obtained from all individual participants included in the study.

Data Availability. Any requests for data by qualified scientific and medical researchers for legitimate research purposes should be submitted in writing to Alfred E. Tiefenbacher GmbH & Co KG, Van-der-Smissen-Straße 1, 22767 Hamburg, Germany.

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