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An Open Label, Balanced, Randomized, Two Treatments, Two Sequences, Two Periods, Single Dose, Cross Over, Oral Bioequivalence Study of Vildagliptin 50 Mg Tablets of Abbott Laboratories De Colombia *vs*. Jalra (Vildagliptin) 50 Mg Tablets of Novartis Pharma Stein Ag, in Healthy, Adult, Human Subjects Under Fasting Condition

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Abstract

Vildagliptin is dipeptidyl peptidase 4 (DPP-4) inhibitors, that inhibits rapid and complete inhibition of DPP-4 activity, resulting in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide) in the treatment of type 2 diabetes mellitus in adults. The purpose of this study was to evaluate the bioequivalence between Vildagliptin 50 mg Tablets of Abbott Laboratories de Colombia *vs*. JALRA (Vildagliptin) 50 mg Tablets of Novartis Pharma Stein AG, in healthy subjects under fasting condition. An open label, balanced, randomized, two treatments, two sequences, two periods, single dose, cross over study with washout period of 03 days under fasting condition was carried out in 42 male subjects in the age group of 19 to 43 years who met the study eligibility criteria, participated in the study and all the 42 subjects completed both periods of the study. The pharmacokinetic samples collected from subjects who completed the study were analysed to determine the plasma concentration of Vildagliptin using bio-analytical method. The 90% confidence interval of C_{max} and AUC_{0-t} were 89.32% - 104.32% and 94.52% - 101.11% respectively which were within the pre-defined acceptable limits and the test product is bioequivalent to the reference product.

Keywords: Vildagliptin • Bioavailability • Bioequivalence • Pharmacokinetic

Abbreviations: AEs: Adverse Events; AUC: Area under the concentration *vs*. time curve; AUC_{0-t}: Area under the plasma concentration *vs*. time curve from zero to time t; BCR: Breakpoint Cluster Region; BMI: Body Mass Index; ECG: Electrocardiogram; EMA : European Medicine Agency; FDA: United States Food and Drug Administration; C_{max} : Concentration Maximum; CV: Coefficient of Variation; IEC: Independent Ethics Committee; mg: Milligram; mL: Millilitre; mM: Milli Molar; ng/mL: Nano gram per millilitre; PK: Pharmacokinetic; T_{max} : Time taken to reach maxim um concentration

Introduction

Many drug patents have recently expired or are scheduled to expire in the near future. In response, many drug manufacturers have expanded their generic drug profile, which requires them to conduct clinical trials that demonstrate that their generic equivalents perform similarly to the innovator drug product. Regulations introduced by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) over the last thirty-five years have strengthened measures to ensure the bioequivalence of drug products, which may be simultaneously manufactured by multiple drug makers. Bioequivalence and bioavailability testing standards have also emerged following recognition that bioequivalence and variations in the bioavailability of drug products can result in therapeutic failure and/or toxicity. Vildagliptin is dipeptidyl peptidase 4 (DPP-4) inhibitors. Vildagliptin rapid and complete inhibition of DPP-4 activity, resulting in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropi polypeptide). This study was designed to evaluate the relative bioavailability of the test Vildagliptin 50 mg Tablets of Abbott Laboratories de Colombia *vs*. reference JALRA (Vildagliptin) 50 mg Tablets of Novartis Pharma Stein AG, in healthy subjects.

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Materials and methods

Materials

Test product, dose and mode of administration, batch: Vildagliptin, 01 x 50 mg, Oral with 200 mL of water in sitting posture under fasting conditions, 9A6332

Reference product, dose and mode of administration, batch: JALRA® (Vildagliptin), 01 x 50 mg, Oral with 200 mL of water in sitting posture under fasting conditions, BLE87.

Methodolgy

The study protocol with annexes was prepared and IEC approval was obtained before initiation of the study. Study subjects were screened and enrolled in the study as per the IEC approved protocol. Written informed consent was obtained from each volunteer for screening prior to initiation of screening procedure and for the study prior to enrolment. Individual counselling was then given to the willing volunteers by the Investigator in private and any questions and concerns were addressed prior to obtaining consent. The Principal investigator/sub-investigator/physician reviewed all the screening results to assess eligibility of each volunteer. Subjects were enrolled in the study based on the inclusion and exclusion criteria. This study was designed based on the known pharmacokinetic profile of the investigational product and general accepted standards for the conduct of bio-equivalence study. Forty-two male subjects who met the eligibility criteria were enrolled and administered with a single dose of either test or reference product in sitting posture at a fixed time in each period and subjects were instructed to maintain sitting posture for 02 hours post dose. Washout of 03 days was maintained between each treatment, in order to minimize any possibility of carryover effect from preceding treatment. The blood samples were collected at pre-defined time intervals for the measurement of pharmacokinetic parameters of Vildagliptin in both the periods. Data obtained from 42 study completers was used for the pharmacokinetic and statistical analysis of Vildagliptin. Bioequivalence was determined by statistical comparison of Ln-transformed data of C_{max} and AUC0-t of the test and reference formulations using SAS® version 9.4 with pharmacokinetic data obtained from 42 study completers [1,2].

Study criteria for inclusion/exclusion of subjects: Healthy volunteers, aged 18 to 45 years, and with BMI of 18.50 - 29.99 Kg/m^2 and weight > 50 Kg were eligible to be enrolled in the study. Inclusion criteria encompassed no evidence of cardiac, pulmonary, gastrointestinal, hepatic, renal, hematologic, or neurologic disorders, or any acute or chronic disease, no history of drug or alcohol addiction, normal laboratory tests (complete blood counts, urinalysis, liver and kidney function, and blood sugar); and serological negativity HIV, hepatitis B. Subjects were informed by an investigator about the purposes and risks of the study. They were asked to abstain from using concomitant medications, including over-the-counter products, dietary supplements and natural products which potentially modify kinetics / dynamics of Vildagliptin, 14 days prior to dosing and throughout the end of the study. Consumption of grapefruit and/or its products were not allowed within 10 days prior to the start of the study. Caffeine and/or xanthine-containing products or alcohol were not allowed 48 hours prior the first administration of the study medications and throughout the blood sampling periods [3].

Sample size and power: For the expected mean difference of 5% between the formulations, with an expected intra-subject CV of 25% for C_{max}, and 14.50% for AUC, ISCV of C_{max} was considered for sample size calculation. Therefore, 37 subjects would be required to prove bioequivalence at 90% power. On the basis of cross over design and considering possible dropouts due to expected adverse drug reaction (ADR), a sample size of 42 subjects was considered for this pivotal bioequivalence study.

Subjects drug administration and blood sampling: After an overnight fasting of 08 hours, subjects were administered with a single oral dose of either test product or reference product with 200 mL of water as per the randomization schedule in sitting posture at ambient temperature in each period. Compliance to drug administration was assessed by examination of the oral cavity and hands of the subject immediately after dosing. Subjects remained in sitting posture for 02 hours after dosing. During this restriction period, the subjects were permitted to walk for reasons such as but not limited to the following: natural exigencies. Subjects were restricted from consumption of water for 01 hour before and 01 hour after dosing in each period and were allowed to drink water ad libitum thereafter. Washout period of 03 days were maintained between the treatments. The pharmacokinetic profile (in terms of rate and extent of absorption) of both test and reference products were evaluated based on measured concentration of drug in the human plasma samples collected during the clinical phase. Blood samples for pharmacokinetic analysis were designed appropriately for characterizing the pharmacokinetic profile for the given treatments at the dose administered. A total of 24 blood samples of 03 mL each at 00.00 hour (pre-dose), 00.25, 00.50, 00.75, 01.00, 01.33, 01.67, 02.00, 02.33, 02.67, 03.00, 03.33, 03.67, 04.00, 04.33, 04.67, 05.00, 05.50, 06.00, 07.00, 08.00, 10.00, 12.00 and 16.00 hours post-dose were collected for measurement of pharmacokinetic parameters in both the periods [4].

Tolerability: Subjects were monitored for adverse events (AEs) during both periods of the study. Subjects were instructed to inform clinic personnel of any untoward medical symptoms and/or events that arose during the study. The Principal Investigator/sub-investigator/ study physician also evaluated the subjects for subsequent dosing. Subject's Safety was assessed *via* continuous monitoring and scheduled recording of safety measurements throughout the study through clinical examinations, vital assessment, 12- lead Electrocardiogram (ECG), clinical laboratory parameters (e.g., Hematology, Biochemistry, Urine analysis and Serology test) and monitoring subjects' well-being, symptoms and signs for adverse events. Safety was evaluated throughout the study and there were no non-serious and serious adverse events reported by subjects following administration of both test and reference products. Both the test and reference products were well tolerated [5-8].

Pharmacokinetic and statistical analysis: Pharmacokinetic and statistical analysis were performed using the concentration data obtained from 42 subjects in fasting conditions who completed both periods of the study.

In order to test the two one-sided tests for bioequivalence, ratio analysis, 90% confidence intervals for the difference between treatments' least-square mean was calculated for Ln-transformed C_{max} and AUC_{0-t} of Vildagliptin.

Pharmacokinetic parameters were calculated using non-compartmental model of Phoneix® WinNolin® version 8.1 and statistical analysis was carried out using the SAS® statistical software, version 9.4 of SAS Institute Inc., USA.

The mean, standard deviation, standard error, geometric mean, coefficient of variation, minimum, median, maximum and range were calculated for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $T_{½}$, K_{el} and $AUC_{Extrapolate}$.

Results and Discussion

Forty-two male subjects in the age group of 19 to 43 years, who met the study eligibility criteria, participated in the study and all the 42 subjects completed both the periods of the study. The clinical phase of the study was conducted over a period of 08 days. Blood sampling was done at pre-defined intervals up to 16.00 hours in both periods, separated by a washout period of 03 days between each period. The plasma concentrations of Vildagliptin were quantified in samples of 42 study completers using a validated bio-analytical method in LC-MS/MS. The pharmacokinetic and statistical analysis of Vildagliptin were performed using the concentration data obtained following analysis of 42 study completers. The results of the statistical analysis of Vildagliptin with the test product were observed to be comparable to that of the reference product.

90% confidence interval of C_{max} and AUC_{0-t} were 89.32% - 104.32% and 94.52% - 101.11%, respectively, which were within the acceptable limits of 80.00% to 125.00% (Figures 1 and 2 and Tables 1-5).

Conclusion

Bioequivalence was demonstrated between Vildagliptin 50 mg Tablets of Abbott Laboratories de Colombia *vs.* JALRA (Vildagliptin) 50 mg Tablets of Novartis Pharma Stein AG in healthy subjects.

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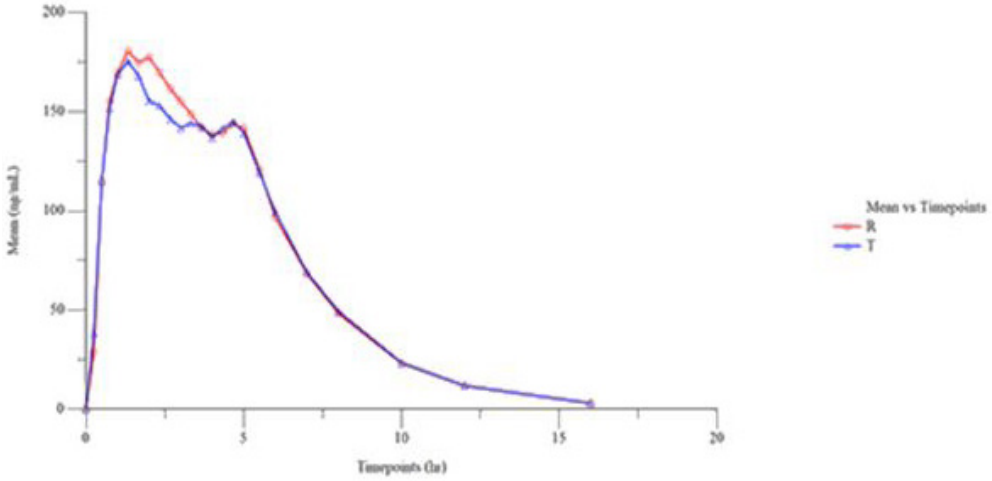

Figure 1. Linear plot of geometric mean plasmatic vildagliptin concentration *vs.* time points (N=42).

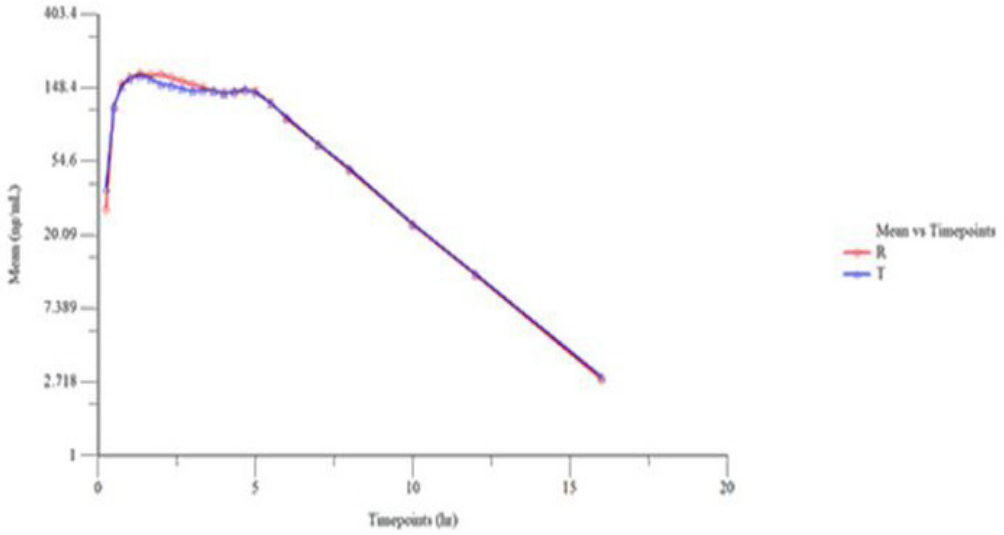

Figure 2. Semilog plot of geometric mean plasmatic vildagliptin concentration *vs.* time points (N=42).

Table 1. Statistical results of test product-t *vs.* reference product-r for vildagliptin (N=42).

Parameters	Antilog Least Square Mean		T/R (%)	90% ConfidenceInterval	Intra subjectCV (%)	Power(%)
	Test Product (T)	Reference Product (R)				
Ln (C_{max})	222.6881	230.6938	96.53	89.32%-104.32%	21.37	99.85
Ln (AUC_{0-t})	1069.6131	1094.1620	97.76	94.52%-101.11%	9.20	100.00

Table 2. Summarized demographic profile of subjects who completed the study for vildagliptin (N=42).

Parameter	Mean	SD	Min	Max
Age (years)	32	6	19	43
Height (m)	1.677	0.053	1.513	1.790
Weight (Kg)	71.3	9.0	54.3	88.6
BMI (Kg/m^2)	25.38	3.01	18.74	29.88

Table 3. Summary of pharmacokinetic parameters for vildagliptin of reference product–R.

Parameter	N	Reference (R)(Mean ± SD)
C_{max} (ng/mL)	42	239.217 ± 64.675
AUC_{0-t} (ng.hr/mL)	42	1115.736 ± 225.248
$AUC_{0-\infty}$ (ng.hr/mL)	42	1130.218 ± 226.754
*T_{max} (hr)	42	1.84 (0.50 – 5.50)
$T_{1/2}$ (hr)	42	0.356 ± 0.068
K_{el} (hr^{-1})	42	2.026 ± 0.453
AUC_% Extrap_Obs(%)	42	1.305 ± 0.755

*Expressed in terms of median (range)

Table 4. Summary of pharmacokinetic parameters for vildagliptin of test Product–T.

Parameter	N	Test (T) (Mean ± SD)
C_{max} (ng/mL)	42	234.005 ± 84.364
AUC_{0-t} (ng.hr/mL)	42	1094.661 ± 239.389
$AUC_{0-\infty}$ (ng.hr/mL)	42	1108.977 ± 240.422
*T_{max} (hr)	42	2.00 (0.50 – 6.00)
$T_{1/2}$ (hr)	42	0.351 ± 0.072
K_{el} (hr^{-1})	42	2.064 ± 0.470
AUC_% Extrap_Obs(%)	42	1.327 ± 0.598
*Expressed in terms of median (range)		

Table 5. P -Value for C_{max} and AUC of vildagliptin.

Parameters	Cmax	AUC_{0-t}	Significance
Sequence effect	0.8329	0.2120	Insignificant for C_{max} and AUC_{0-t}
Period effect	0.3916	0.8334	Insignificant for C_{max} and AUC_{0-t}
Treatment (Formulation) effect	0.4482	0.2639	Insignificant for C_{max} and AUC_{0-t}
Subjects nested within sequence	0.0007	<.0001	Significant for C_{max} and AUC_{0-t}
P < .10 for Sequence effect and P < .05 for all other effects considered to be significant.			

Novartis Pharma Stein AG in healthy subjects.

References

1. Guideline, ICH Harmonised Tripartite. "Guideline for good clinical practice." *J Postgrad Med* 47 (2001): 199-203.
2. ICH, E3. "Structure and content of clinical study reports." In London, UK: International Conference on Harmonisation (1995).
3. Dubey, Akhilesh, Bhasini Kotian and Ravi Gundadka Shriram. "New drugs and clinical trials rules, 2019: Towards fast-track accessibility of new drugs to the indian population." *Indian J Pharm Educ* Res 53 (2019): S451-S459.
4. Schütz, Helmut, Detlew Labes and Martin J. Wolfsegger. "Critical remarks on reference-scaled average bioequivalence." *J Pharm Pharm Sci* 25 (2022): 285-296.
5. INVIMA's Resolution 00001124, Ministry of Health and Social Protection (2016).
6. Notestein, Frank B., Carl W. Hubman and James W. Bowler. "Geology of the barco concession, republic of Colombia, South America." *Geol Soc Am Bull* 55 (1944): 1165-1216.
7. Food and Drug Administration. "21 Code of federal regulations." Part 21 current good manufacturing practice for finished pharmaceuticals United State (1994).
8. Schnaars, Yvonne, Sumedh Gaikwad, Ulrike Gottwald-Hostalek and Ulrike Klingberg, et al. "Bioequivalence studies of new generic formulations of vildagliptin and fixed-drug combination of vildagliptin and metformin *vs.* respective originator products in healthy volunteers." *Diabetes Therapy* 13 (2022): 1215-1229.

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