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A BIOEQUIVALENCE STUDY OF TRELAGLIPTIN 100 MG TABLETS IN HEALTHY VOLUNTEERS: AN OPEN-LABEL, RANDOMIZED, TWO-TREATMENT, TWO-PERIOD, SINGLE-DOSE, CROSSOVER STUDY

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ABSTRACT

Background: Once-weekly therapies like Trelagliptin, a long-acting Dipeptidyl Peptidase-4 (DPP-4) inhibitor, can enhance medication adherence and simplify treatment. Pharmacokinetic data on Trelagliptin in Indians are limited, necessitating a bioequivalence study with the reference product for regulatory approval and therapeutic consistency. **Objective:** To evaluate the pharmacokinetics and bioequivalence of the test product, Trelagliptin 100 mg tablet of Zuventus Healthcare Limited, compared to the reference product, Zafatek® (Takeda Pharmaceutical Company Limited, Japan), in healthy Indian adults under fasting conditions. **Methods:** This was an open-label, randomized, two-treatment, two-period, crossover, single-dose, truncated, bioequivalence study with a 25-day washout period. Pharmacokinetic parameters (C_{max}, AUC_{0-72}, T_{max}) were assessed up to 72 hours post-dose. Plasma concentrations were measured using a validated liquid chromatography-tandem mass spectrometry (LC–MS/MS) method. Bioequivalence was established if the 90% confidence intervals (CI) of the geometric mean ratios (GMRs) for log-transformed primary parameters, C_{max} and AUC_{0-72} fell within the 80.00–125.00% acceptance range. **Results:** Thirty-two male volunteers were enrolled, and 31 completed the study. The test and reference products demonstrated comparable pharmacokinetic profiles. The GMRs were 104.55% and 102.31% for C_{max} and AUC_{0-72}, respectively. The intra-subject coefficient of variation (ISCV) was 23.04% for C_{max} and 4.25% for AUC_{0-72}. The 90% CI for Trelagliptin was 94.77–115.34% for C_{max} and 100.45–104.20% for AUC_{0-72}, falling within the accepted bioequivalence range. Both products were well-tolerated, with only mild adverse events reported. **Conclusions:** Trelagliptin 100 mg tablet of Zuventus Healthcare Limited is bioequivalent to the Originator Product, Zafatek® from Japan and well-tolerated in healthy Indian subjects.

KEYWORDS: Bioequivalence, Dipeptidyl Peptidase-4 inhibitor, Once-weekly, Oral antidiabetic, Trelagliptin.

1. INTRODUCTION

Poor medication adherence and a high pill burden are key factors that hinder effective glycemic control in type 2 diabetes mellitus (T2DM).[1,4] Nearly two-thirds of diabetic Indian patients fail to achieve optimal glycemic control.[5] A 10% rise in non-adherence is associated with a 0.14% increase in glycated hemoglobin (HbA1c) and contributes to a 4.9 mg/dL increase in low-density lipoprotein cholesterol.[6] These factors substantially impair glycemic management and elevate cardiovascular risk.

Daily dose regimens may offer glycemic control but may require more effort to ensure proper adherence and can result in a higher burden on patients. Reducing dosing frequency and extending drug action simplifies treatment regimens and improves patient adherence. The use of a once-weekly regimen is effective and well-tolerated in diabetes treatment and improves treatment compliance.[7,8]

Trelagliptin is the first long-acting Dipeptidyl peptidase-4 (DPP-4) inhibitor designed to enhance glycemic

control by prolonging its action.[9] Its extended half-life of 54.3 hours is primarily due to its strong and prolonged binding to the DPP-4 enzyme, facilitated by the fluorine atom at the 5-position of the cyanobenzyl group.[10,11] This modification enhances its stability and reduces its enzymatic dissociation rate, resulting in slower clearance from the body and enabling sustained pharmacological activity for 1 week.

Once-weekly Trelagliptin showed comparable efficacy to daily DPP-4 inhibitors (Alogliptin, Sitagliptin, Vildagliptin)[12-14] with a favourable safety profile.[15-17] It has also shown effectiveness in combination with insulin and other antidiabetic therapies.[18,19] Trelagliptin has been approved in Japan for the treatment of T2DM.[20] In this study, a formulation of Trelagliptin developed by Zuventus Healthcare Limited, India was evaluated to assess the pharmacokinetics and safety of a single 100 mg dose, demonstrating bioequivalence in healthy Indian adults under fasting conditions. Based on these findings and supporting clinical trial data, Trelagliptin was approved by Central Drugs Standard Control Organisation (CDSCO), India.

2. MATERIALS AND METHODS

2.1 Ethical Consideration

The study protocol and informed consent documents were reviewed and approved by the Institutional Ethics Committee (Reg. No.: ECR/139/Inst/AP/2013/RR-19) and Central Licensing Authority (BENOC No.: BE/ND/30/2022) before study initiation. Informed written consent was obtained from all participants before their enrolment. The study adhered to the principles outlined in the Declaration of Helsinki,[21] Good Clinical Practices guidelines[22], Bioavailability and Bioequivalence guidelines,[23,24] Indian Council of Medical Research guidelines,[25] and New Drugs and Clinical Trials Rules 2019, India.[26]

2.2 Study Population

This study enrolled healthy volunteers aged 18 to 45 years with a body mass index (BMI) ranging from 18.5 to 29.9 kg/m^2. Eligibility screening was conducted within 21 days prior to enrolment. These included general medical history such as prior participation in clinical trials, history of blood donation, and patterns of alcohol or tobacco use alongside demographic data, medical history, and a physical examination. Assessments encompassed vital signs, electrocardiogram, chest X-ray, hematology, biochemistry, and urinalysis. Additionally, participants were tested for HIV I and II, as well as hepatitis B and C. Female participants qualified if they were neither pregnant nor breastfeeding and committed to using reliable contraception methods. Exclusion criteria included the use of any medications within 14 days prior to dosing, hypersensitivity to Trelagliptin or any drugs in its class, clinically significant systemic or local diseases, any condition that could interfere with the pharmacokinetics of the investigational product and any clinically significant abnormality in laboratory test results.

2.3 Study Design and Procedures

This was an open-label, randomized, two-treatment, two-sequence, two-period, single-dose, truncated, crossover oral bioequivalence study (Study Registry No.: CTRI/2023/01/048758) under fasting conditions. This study was carried out between March 2023 to April 2023 at Advity Research (P) Limited, Hyderabad (Reg. No.: BABE/2022/0103).

In each period, subjects received either Test product (T), Trelagliptin 100 mg tablets of Zuventus Healthcare Limited, India (Trelaglip®) or Reference product (R), Zafatek® (Trelagliptin 100 mg) tablets of Takeda Pharmaceutical Company Limited, Japan, following a fasting period of at least 10 hours before dosing. Subjects were assigned to one of two sequences (T-R or R-T) based on a randomization schedule. The randomization code was generated by SAS® (version 9.4). To ensure the complete elimination of Trelagliptin[11], a washout period of 25 days was maintained between consecutive doses.

Study subjects were confined to the study facility for at least 11 hours before dosing and remained there for a minimum of 72 hours after dosing. They underwent an overnight fast of at least 10 hours, which continued for at least 4 hours following dosing. For the next 2 hours after dosing, subjects remained in a resting and sitting position. Water intake was restricted to 1 hour before dosing. A single oral dose of the assigned product was administered to subjects with 240 mL of a 20% glucose solution, followed by 60 mL of the same solution every 15 min for up to 4 hours post-dosing. Thereafter, water was freely available to the subjects.

A total of 24 venous blood samples (5 mL) were collected at pre-dose, at 0.17, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours post-dose in vacutainers containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) during each study period. All samples were centrifuged at 3500 rpm for 10 minutes at 4^{o}C within 45 minutes of collection. An aliquot of the separated plasma was transferred into two pre-labelled polypropylene tubes and stored upright at -70±15°C.

2.4 Bioanalytical Method

The bioanalysis complied with Good Laboratory Practice principles using a validated LC-MS/MS method.[27] Plasma Trelagliptin concentrations were determined with a Shimadzu HPLC system (LC-40 Series) coupled to a Sciex 4500 triple quadrupole mass spectrometer. A 0.1 mL plasma aliquot containing the analyte and internal standard underwent liquid-liquid extraction. The extracted supernatant (10 µL) was injected into the system equipped with a Kinetex® Evo C18 column (100 × 4.6 mm, 5 µm, 110 Å, Phenomenex), using a mobile

phase of methanol:0.2% acetic acid (60:40) at a flow rate of 0.9 mL/min. Detection was performed in positive-ion mode using electrospray ionization (ESI) and multiple reaction monitoring (MRM). The monitored transitions were m/z 358.1 → 341.1 for Trelagliptin and m/z 362.2 → 345.1 for the internal standard (Trelagliptin-13C-D3). The loss of NH_3 resulted in a difference of 17 Da in the mass-to-charge ratio (m/z). This transition was based on its specificity and sensitivity, in alignment with previously published studies.[28-30]

2.5 Pharmacokinetic parameters

A truncated design (considering the long half-life of Trelagliptin) was employed, with the pharmacokinetic assessment up to 72 hours post-dose to capture the key parameters. The primary pharmacokinetic parameters were peak plasma concentration (C_{max}) and area under the concentration-time curve from time zero to 72 hours (AUC_{0-72}), calculated using the linear trapezoidal method. Secondary pharmacokinetic parameters included time to peak concentration (T_{max}). Values below the lower limit of quantification (LLOQ) were treated as zero for pharmacokinetic and statistical analysis and missing or non-reportable values were excluded from the parameter calculations.

2.6 Statistical Methods

The statistical analysis of ln-transformed pharmacokinetic parameters (C_{max} and AUC_{0-72}) for Trelagliptin was performed using SAS® Version 9.4 (SAS® Institute Inc., USA). A PROC GLM analysis of variance (ANOVA) model was used with treatment, period, sequence, and subject (nested within sequence) effects. The sequence effect was tested at a 0.10 significance level and other effects at 0.05. For C_{max} and AUC_{0-72}, a two one-sided test was applied to calculate 90% confidence intervals (CIs) using ln-transformed data. The bioequivalence was established if the 90% CI was within the acceptance range of 80.00%- 125.00%. Bioequivalence was assessed in 32 subjects, considering a 16.8% intrasubject variability for C_{max}, a geometric mean ratio (T/R) of 0.9, 80% power, and a 0.05 significance level.

3. RESULTS

3.1 Demographic Characteristics

Thirty-two eligible male subjects were enrolled in the study, with a mean age of 32.44 ± 5.81 (range 21-44) years and a BMI of 25.33 ± 2.35 (range 19.5-29.5) kg/m^2. One subject dropped out in the second period. The pharmacokinetic and statistical analysis was performed on the 31 subjects who completed both study periods and were assessed for bioequivalence (Figure 1).

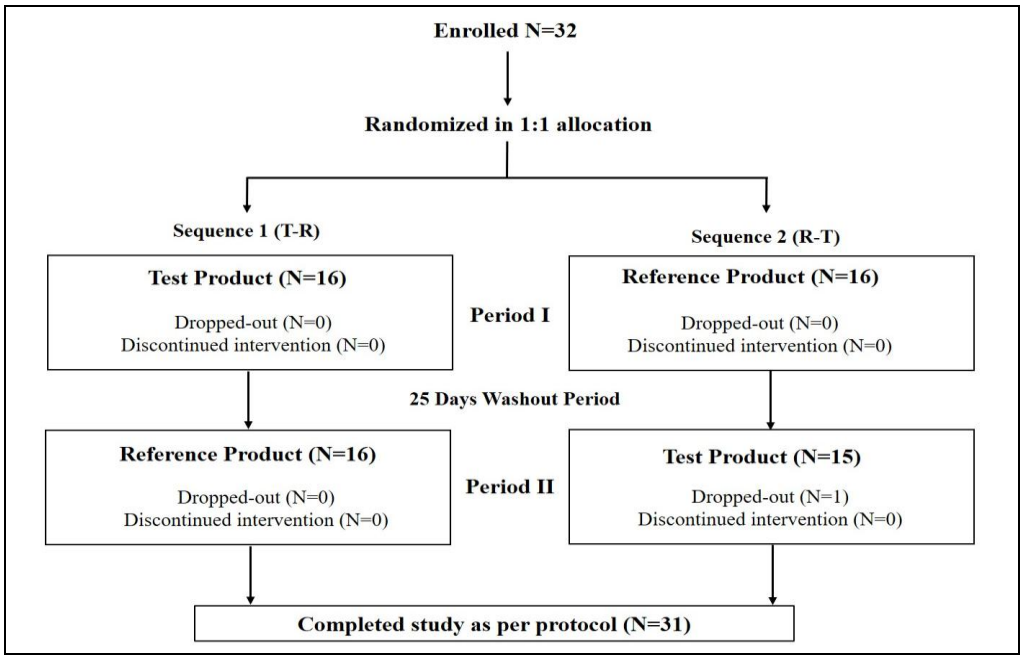

Figure 1: Disposition of subjects.

3.2. Bioanalytical Method Validation

The bioanalytical method was validated for Trelagliptin quantification in human plasma (5.000–1502.042 ng/mL) using weighted $1/X^2$ regression with an LLOQ of 5 ng/mL. The goodness of fit for linearity was >0.99. Linearity was demonstrated for all standard curves with correlation coefficients (r) > 0.999 and regression coefficients (r^2) > 0.999, meeting the regulatory criteria. The intra- and inter-batch accuracy ranged from 94.9% to 98.1% and from 94.9% to 98.0%, respectively, with precision variability of 4.3%. The recovery of Trelagliptin was 82.4 % and for the internal standard was 91.5%. The stability study showed that Trelagliptin in plasma was stable for 20 hours at room temperature (98.4%), at 2-8°C for 69 days (99.8%), and after five freeze-thaw cycles. The autosampler stability for Trelagliptin was for 34 hours, while its bench-top stability was confirmed for 21 hours.

3.3 Pharmacokinetics and Statistical Evaluation

Figure 2 presents the overlapping mean plasma concentration-time profile following oral administration of Trelagliptin. The Trelagliptin was rapidly absorbed, with mean peak plasma concentrations of 437.55 ng/mL for the test product at a mean time of 3.50 hours. With the reference product, the corresponding values were 429.03 ng/mL at a mean time of 3.00 hours. The total drug exposure over 72 hours was similar between the two products. The AUC_{0-72} values were 6710.97 ng·hr/mL for the test and 6558.39 ng·hr/mL for the reference. The data are shown in Table 1.

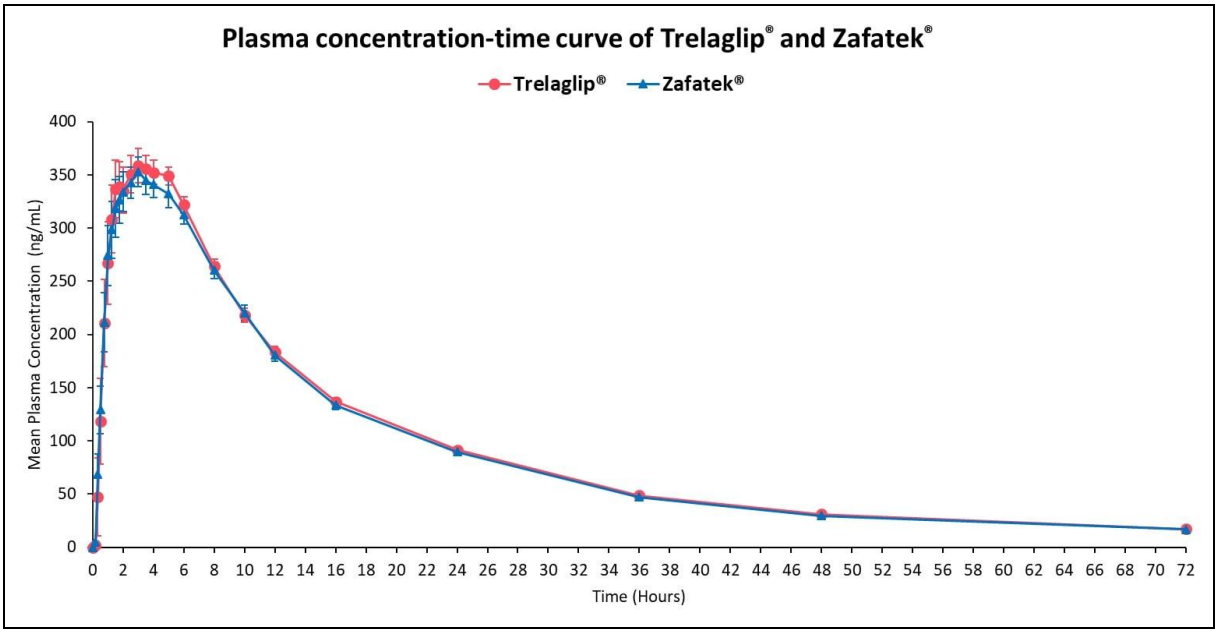

Figure 2: Mean plasma concentration-time profile of Trelagliptin

Table 1: Pharmacokinetic parameters of Trelagliptin.

	Arithmetic mean ± SD (%CV), N = 31	
	Test	**Reference**
C_{max} (ng/mL)	437.55 ± 120.449 (27.53)	429.03 ± 174.309 (40.63)
AUC_{0-72} (ng.hr/mL)	6710.97 ± 797.947 (11.89)	6558.39 ± 795.249 (12.13)
T_{max} (h)*	3.50 (0.33 - 6.00)	3.00 (0.33 - 6.00)

CV: coefficient of variation, SD: standard deviation,
** For T_{max}: median (range)*

The analysis of ln-transformed C_{max} and AUC_{0-72} showed that the effects of sequence, period, and formulation were not significant. The subject effect within sequences was significant, indicating variability among subjects, but this is expected and typical in bioequivalence studies due to individual differences in pharmacokinetics as shown in Table 2.

Table 2: Analysis of variance for the C_{max} and AUC_{0-72}.

	Effect	**Sum of squares**	**df**	**Mean sum of squares**	**F**	**p**
C_{max} (ng/mL)	Formulation	0.03065691	1	0.03065691	0.59	0.4477
	Sequence	0.04019244	1	0.04019244	0.32	0.5770
	Period	0.00994448	1	0.00994448	0.19	0.6644
	Subject (Sequence)	3.66339173	29	0.12632385	2.44	0.0095
AUC_{0-72} (ng.hr/mL)	Formulation	0.00807348	1	0.00807348	4.48	0.0429
	Sequence	0.00970836	1	0.00970836	0.36	0.5513
	Period	0.00245803	1	0.00245803	1.36	0.2522
	Subject (Sequence)	0.77459622	29	0.02671021	14.83	<.0001

Table 3 presents the geometric mean ratio and 90% CI for the ln-transformed values of C_{max} and AUC_{0-72}. The intra-subject coefficient of variation (ISCV) was 23.04% for C_{max} and 4.25% for AUC_{0-72}, demonstrating low variability (<30%). The 90% CIs for C_{max} (94.77-115.34) and AUC_{0-72} (100.45-104.20) fell within the accepted bioequivalence range of 80.00% to 125.00%.

Table 3: Ratio analysis and 90% confidence intervals.

	Geometric LS mean (N=31)						
	Test	**Reference**	**T/R ratio (%)**	**ISCV (%)**	**Power (%)**	**90% CI**	**Conclusion**
LnC_{max} (ng/mL)	422.78	404.38	104.55	23.04	98.05	94.77-115.34	Bioequivalent
$LnAUC_{0-72}$ (hr.ng/mL)	6662.06	6511.66	102.31	4.25	99.99	100.45-104.20	Bioequivalent

CI: confidence interval, ISCV: intra-subject coefficient of variance, LS: least square

3.4 Safety Results

Trelagliptin was well-tolerated among the study participants, with a total of five adverse events (AEs) reported. Three AEs, including giddiness, fever, and nausea, were identified during clinical examinations, while two were found through laboratory analysis (elevated AST & ALT and increased amylase levels). All AEs were mild in intensity and not accompanied by any other complications.

4. DISCUSSION

This study highlights the findings on the pharmacokinetics of Trelagliptin in Indian healthy participants. The study objectives were to evaluate the comparative pharmacokinetics and conclude the bioequivalence of generic formulation with Japanese reference product. The study was conducted under fasting conditions as it is considered to be the most sensitive to detect significant differences between formulations.[24] According to a food effect study, food intake does not affect the pharmacokinetics or pharmacodynamics of Trelagliptin.[11]

Trelagliptin is a structural analogue of Alogliptin, designed with modifications to enhance its binding affinity, which improved its pharmacokinetic profile. Due to the long half-life (>24 hours), AUC truncated at 72 hours (AUC_{0-72}) was used to assess exposure in line with regulatory guidelines.[23,24] Despite the extended study duration, including a 25-day washout period, the dropout rate was lower than expected. ANOVA analysis showed no carryover from the previous dose, confirming that the 25-day washout period was sufficient for complete drug elimination between doses.

The pharmacokinetic profiles of both formulations were comparable. The study had adequate power to identify any potential differences between the investigational products. Furthermore, ANOVA analysis for C_{max} and AUC_{0-72} showed no significant difference across sequence, period, or formulation factors. The geometric mean ratios were close to 1, supporting bioequivalence between the test and reference product. This was further confirmed by the 90% CI for the GMRs of C_{max} and $AUC_{0–72}$, which fell within the accepted bioequivalence range of 80.00–125.00%. The safety profile of the Trelagliptin 100 mg tablets was favorable, with no serious adverse events reported. The safety findings align with the established safety profile outlined in the Prescribing Information of the innovator product,[20] indicating no new safety concerns in the studied population.

In an *in-vitro* study,[10,31] in healthy subjects[11,32] in T2DM patients[11,33], Trelagliptin plasma concentrations 1.4–2.3 ng/mL at 168 hours were shown to inhibit plasma DPP-4 activity by 70–81.3%. For the test product, the extrapolated plasma concentration of Trelagliptin at 168 hours was 1.67 ng/mL, while 1.84 ng/mL for the reference. These concentrations are sufficient to sustain the pharmacodynamic effect over 7 days. No accumulation was reported on repeated dosing.[11] Additionally, a meta-analysis demonstrated that it provides good glycemic control and is comparable to daily-dosing DPP-4 inhibitors.[34] Therefore, based on its pharmacokinetic and pharmacodynamic profile, a once-weekly dosing regimen is supported for Trelagliptin. Future studies could explore the pharmacokinetic profile in special populations to further expand its clinical utility.

5. CONCLUSIONS

The study demonstrates that Trelagliptin 100 mg tablets developed by Zuventus Healthcare Limited are bioequivalent to the reference product, Zafatek® (Takeda, Japan), under fasting conditions in healthy Indian adults. Both formulations exhibited similar pharmacokinetic profiles and were well-tolerated, indicating that the Trelagliptin can be considered a therapeutically equivalent alternative for clinical use in the Indian population.

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None.

ETHICAL STATEMENT

The study was approved by the CDSCO, India, and the Institutional Ethics Committee of the study centre. The trial was conducted in compliance with the Guidelines for Good Clinical Practice and the Declaration of Helsinki principles. Written informed consent was obtained from all participants.

CONFLICT OF INTEREST

There are no conflicts of interest.

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