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Research Article

A Randomized, Open-Label, Crossover Trial to Assess Bioequivalence of Teneligliptin 10 mg Twice-Daily with Teneligliptin 20 mg Once-Daily

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Abstract

Background: Teneligliptin is an oral antidiabetic drug that inhibits the dipeptidyl peptidase-4 enzyme and available dosage regimen of teneligliptin is 20 mg once-daily. An alternative twice-daily medication regimen having similar glycemic control is required to explore the fixed-dose combination with other antidiabetic drugs. **Methods**: This open-label, crossover study compared pharmacokinetics and pharmacodynamics of teneligliptin 20 mg once-daily (reference) and 10 mg twice-daily (test) at a steady state under fasting conditions administered for seven days. Primary endpoints assessed bioavailability based on 24-hour exposure (area under the curve) between two dosages at a steady state; secondary endpoint(s) included plasma DPP-4 inhibition profile over 24 hours and safety between the two dosage regimen. **Results**: A total of 28 healthy adult male subjects were enrolled, and all completed the study. Steady state exposure over 24-h (area under the curve $_{0–24ss}$) was similar for teneligliptin 20 mg once-daily and 10 mg twice-daily (1981.1 versus 1965.9 ng hr/mL) and 90% confidence interval of the adjusted geometric mean ratio of area under the curve $_{0–24ss}$ was well within the acceptable range for bioequivalence (99.3% ratio; 90% confidence interval [95.89-102.82]). Maximal dipeptidyl peptidase-4 inhibition at steady state over 24-hour interval was 85.4% and 89.0% with teneligliptin 10 mg twice-daily and 20 mg once-daily, respectively. Both dosage regimens resulted in a dipeptidyl peptidase-4 inhibition ≥80% at trough. No adverse events were reported throughout the study. **Conclusion**: Teneligliptin 20 mg once-daily and 10 mg twice-daily were found bioequivalent with similar dipeptidyl peptidase-4 inhibition.

Keywords: Bioequivalence; Fixed-dose combination; Pharmacokinetics; Pharmacodynamics; Teneligliptin, Type II diabetes

Abbreviations: AE: Adverse events; ANOVA: Analysis of Variance; AUC: Area under the curve; $AUC_{DPP4inh}$: AUC of DPP-4 inhibition curve; $AUC_{DPP4inh}$/dosing interval: Average inhibition effect over the dosing period; b.i.d.: Twice daily; BMI: Body Mass Index; $C_{max,ss}$: Maximum plasma concentration over a 12- or 24-h period at steady state; CDSCO: Central Drugs Standard Control Organization; CHF: Congestive Heart Failure; CYP3A4: Cytochrome P450 3A4; DPP-4: Dipeptidyl peptidase-4; FDC: Fixed-dose combination; FMO3: Flavin-containing monooxygenase 3; IC50: Half-maximal inhibitory concentration; I_{max}: Peak DPP-4 inhibition; I_{trough}: Trough level inhibition; LS: Least-square; PD: Pharmacodynamic; PK: Pharmacokinetic; $T_{max,ss}$: Time to reach maximum concentration at steady state; T_{Imax}: Time to reach I_{max}; T2DM: Type II diabetes mellitus; q.d.: Once daily

Introduction

Globally, prevalence of type II diabetes mellitus (T2DM) is increasing rapidly due to the lifestyle changes. [1] The International Diabetes Federation 2021 report forecasts the total number of people with diabetes to reach 783 million worldwide by 2045 [2]. As a matter of fact, antidiabetic medications providing stable anti hyperglycemic effect and good safety profile becomes critical to effective patient management strategies [3].

Of the several drugs available to manage T2DM, dipeptidyl peptidase-4 (DPP-4) inhibitors are preferred due to their glucose-lowering ability with minimal risk of hypoglycemia [4]. Teneligliptin, a selective DPP-4 inhibitor, is available as an oral antidiabetic agent since 2012 with an established efficacy and safety profile in subjects with T2DM [5]. Teneligliptin has a half-life of approximately 24 hours with distinctive pharmacokinetic (PK) properties. It has moderate selectivity to DPP-4 receptors and inhibits concentration-dependent human plasma DPP-4 activity. Its half-maximal inhibitory concentration (IC50) value is approximately160-850 times higher vs. other DPP-4 enzymes [6]. It is metabolized by cytochrome P450 3A4 (CYP3A4) and flavin-containing monooxygenase 3 (FMO3) in liver or excreted in an unchanged form via the kidney (34.4% via urine and 65.6% via bile) [7]. Due to its multiple elimination pathways, it requires no dosage adjustment in subjects with hepatic or renal impairment [8].

Established evidence exists amongst Asian countries on teneligliptin's efficacy and tolerability either as a monotherapy or in combination with antidiabetic medications, including metformin and sulfonylurea [6,9-13]. In several clinical trials, teneligliptin was administered 10, 20, and 40 mg once daily (q.d.) either as a monotherapy or in combination with other drugs [9,11,14-19]. Currently, the recommended dosage of teneligliptin is 20 mg q.d. [7]. Many commonly administered antidiabetic medications such as metformin are given as twice daily (b.i.d.) regimen. [20] Moreover, several previous studies have advocated a combination of metformin and DPP-4 inhibitors as a second-line treatment option [21]. The twice daily regimen of teneligliptin would allow rational fixed-dose combination (FDC) with other twice daily regimen antidiabetic medications which will provide convenience, enhance treatment adherence and compliance in T2DM subjects. The PK profile of teneligliptin suggests that the drug could be administered in a b.i.d. regimen and hence, FDC with other twice daily administered antidiabetic medication is possible.

Therefore, we planned a steady state PK and pharmacodynamic (PD) analysis to determine the bioequivalence of the orally administered teneligliptin 10 mg b.i.d. relative to 20 mg q.d. Our treatment strategy is expected to enhance patient convenience and compliance, resulting in better glycemic control in subjects with T2D.

Materials and Methods

Study design and participants

This was an open-label, randomized, two-period, repeat dose, two-way, crossover, steady-state comparative PK/PD study of teneligliptin in healthy male subjects aged 18-45 years under fasting conditions. The study was conducted between March 2020 to June 2020 at the clinical facility of Panexcell Clinical Lab Private Limited, Mumbai.

The subjects were screened at least 28 days before the administration of treatment. Healthy, adult male subjects with a Body Mass Index (BMI) between 18.5-29.9 kg/m^2, body weight ≤50 kg, who have ability to fast for at least 8 hours and who provided the informed consent for participation in the study were included. Subjects were excluded if they had: history or evidence of hypersensitivity to teneligliptin; presence or history of a clinically significant disorder involving the cardiovascular (ventricular dysfunction such as Congestive Heart Failure [CHF] or a history of CHF), musculoskeletal, respiratory, renal, urologic, gastrointestinal, hepatic, immunologic, hematologic, endocrine, or neurologic system(s) or psychiatric disease as determined by the investigator(s); participation in any clinical trial within 90 days of study participation; family history of neurological disorders; record of dehydration due to diarrhea, vomiting or any other reason within 24 hours before study check-in and throughout the study. Detailed inclusion and exclusion criteria are described in Table 1. The study was conducted in compliance with ethical guidelines for biomedical research on human participants, Indian Council of Medical Research 2017, International Conference on Harmonization-Good Clinical Practice (ICH-GCP) E6 (R2) (Step 4) Guidance on Good Clinical Practice, New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E) of Central Drugs Standard Control Organization (CDSCO), Good Laboratory Practice, Good Clinical Practices for Clinical Research in India Guidelines, Declaration of Helsinki (Fortaleza, October 2013), and Guidelines for Bioavailability and Bioequivalence studies, CDSCO India. The independent ethics committee reviewed the clinical trial protocol, informed consent, and related documents.

Inclusion Criteria	Exclusion Criteria
1. Healthy adult human male subjects aged 18–45 years. 2. Subjects with a BMI ranging from 18.50–29.90 kg/m^2 and body weight not less than 50 kg. 3. Completed the screening process within 28 days before period I dosing. 4. Subjects in normal health as determined by personal medical history, clinical examination including vital signs, and clinically acceptable results of laboratory examinations. 5. Subjects having a normal or clinically non-significant 12-lead electrocardiogram recording and serum electrolytes. 6. Subjects who are willing to refrain from driving and using heavy machinery. 7. Subjects having clinically acceptable chest X-Ray if taken. 8. The subject has understood and signed the informed consent form to participate in the study. 9. Subjects willing to adhere to the protocol requirements. 10. Ability to fast for at least 8 hours.	1. History or evidence of hypersensitivity to teneligliptin. 2. Presence of any clinically significant results from laboratory tests, vital signs assessments, medical examination, and ECG, as judged by the investigator(s). 3. Report any presence or history of a clinically significant disorder involving the cardiovascular (ventricular dysfunction such as CHF or a history of CHF), musculoskeletal, respiratory, renal, urologic, gastrointestinal, hepatic, immunologic, hematologic, endocrine, or neurologic system(s) or psychiatric disease as determined by the investigator(s). 4. Demonstrates a positive test result for hepatitis B surface antigen, hepatitis C antibody or HIV antibody, VDRL. 5. History or presence of significant smoking more than 10 cigarettes/day. 6. History of difficulty with donating blood. 7. History of addiction to any recreational drug or drug dependence. 8. Donation of blood (350 mL) within 90 days before the start of the study. 9. Participation in any clinical study within the past 90 days. 10. Receipt of any prescribed medications within 7 days before study start. 11. Receipt of any herbal remedies and any OTC medications (including herbal remedies) within 14 days before study start. 12. History of dehydration from diarrhea, vomiting, or any other reason within 24 hours before study check-in and throughout the study. 13. Family history of neurological disorders. 14. An unusual or abnormal diet within 48 hours before study check-in of the study period, for whatever reason, e.g., fasting due to religious reasons. 15. Consumption of chewing tobacco, pan or pan masala, gutkha, masala (containing betel nut and tobacco) for at least 24 hours before check-in. 16. Consumption of alcoholic products, xanthine-containing foods or beverages (i.e., coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) or potent inhibitors of PGP/CYP3A4, grapefruit and/or its juice and poppy containing foods for at least 72.00 hours before check-in. 17. Positive results for urine screen for drugs of abuse (Amphetamine, Barbiturates, Marijuana, Cocaine, Morphine, Benzodiazepines) during the study check-in. 18. Positive results for alcohol breath analysis during the study check-in period.

BMI: Body mass index; CHF: Congestive Heart Failure; CYP3A4: Cytochrome P450 3A4; ECG: Electrocardiogram; HIV: Human Immunodeficiency Virus; OTC: Over-The-Counter Medications; PGP: P-Glycoprotein; VDRL: Venereal Disease Research Laboratory.

Table 1: Inclusion and Exclusion Criteria.

Study treatment and procedures

During period I of the study, subjects were randomized to receive teneligliptin 10 mg b.i.d (test treatment) or teneligliptin 20 mg q.d. (reference treatment). After switchover, period II started without any washout period. The study treatment was administered orally for seven days each during both study periods (using two sequences) with 240 mL of 20% aqueous glucose solution at ambient temperature; the treatment administration was preceded by an overnight fast of at least 8 hours before morning dose and 3 hours before evening dose.

Sample collection and processing

During period I, a pre-dose blood sample (4 mL) was collected within an hour before dosing on Day 1 to assess the pre-dose concentration of teneligliptin; two blood samples (3 mL) were collected at 1 hour and 2 hour respectively, before dosing on Day 1 for all the subjects to define PD analysis as 0% inhibition; one blood sample (4 mL) was collected within 10 minutes before dosing on Day 1, 5, 6, and 7 for all the subjects to define the PK steady state.

Sampling schedule for PK/PD analysis of the test product (Teneligliptin 10 mg): On Day 7 of each study period, a total of 22 blood samples (7 mL each) were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 11.75 hour post-dose (both morning and evening dose) in pre-labeled pre-chilled vacutainers containing dipotassium ethylene diamine tetra acetic acid (K2-EDTA) as an anticoagulant.

Sampling schedule for PK and PD sample analysis for the reference product (Teneligliptin tablets 20 mg): On Day 7 of each study period, a total of 12 blood samples (7 mL each) were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 hour post-dose in pre-labeled pre-chilled vacutainers containing K2-ethylenediamine tetraacetic acid (EDTA) as an anticoagulant.

The collected blood samples placed in a wet ice bath until were centrifuged within 60 minutes of blood sample collection and spun at 3800 rpm at 10 ˚C for 10 minutes to separate the plasma. Plasma samples were stored at −70±10 ˚C before and after analysis for measuring the concentration of teneligliptin in plasma. The interval between the first sample collection for each time point and placement of plasma sample in the deep freezer did not exceed 90 minutes.

Safety measurements

The safety measurements included clinical laboratory parameters, vital signs, and adverse event (AE) monitoring. All the safety parameters were recorded at the time of screening and specified study intervals (Supplementary Table 1).

Activities	Screening (28 days)	Period I		Period II	
		Check-in (Day 00)	Inhouse period (Day 1-7)	Inhouse period (Day 8-14)	Check-out (Day 15)
Medical history	**D**				
Medical examination	**D**	**D**		**D**	
Vitals	**D**	**D**	**D**	**D**	**D**
Screening Consent	**D**	**D**			
Study specific Consent	**D**	**D**			
Patient Wellbeing Record	**D**	**D**	**D**	**D**	**D**
Dosing			**D***	**D***	
Monitoring for medical (Unfavourable) event		**D**			
Monitoring for AE			**D**	**D**	**D**
Screening Lab tests	**D**	**D**			
Meal distribution		**D**	**D**	**D**	
Blood Samples collection	**D**		**D****	**D****	**D**
ECG	**D*****				**D*****

Urine screen for drug of abuse		**D**			
Alcohol breath test		**D**			
Chest X-Ray[#]	**D**				
Post Study safety assessment					**D**[****]
Blood Glucose Level Monitoring			**D**[*****]	**D**[*****]	

D, study events assessment done
D[*], Dosing was done from Day 01 to Day 14, either test product (BID regimen) or reference product (once daily) was administered as per randomization schedule in both the periods.
D[**], Sampling Collection was done on Day 07 in the both the periods.
D[***], ECG was recorded at the time of screening and end of the study 24.00 hours post dose in period – II and/or in case of patient is withdrawn or dropped-out from the study, or in case of termination of the study.
D[****], Post study was performed at 24.00 hours post dose of period – II or in case of patient is withdrawn or dropped-out from the study, or in case of termination of the study.
D[*****], Blood glucose level was monitored prior to dosing and at 01.00, 03.00 and 05.00 hours from morning dosing and at 01.00, 03.00 and 05.00 hours from evening dosing of test product (± 30 minutes) from Day 01 to Day 07 and additionally when required at the discretion of the Investigator. Blood glucose level was monitored prior to dosing and at 01.00, 03.00, 08.00 and 10.00 hours (± 30 minutes) post dose of reference product from Day 01 to Day 07 and additionally when required at the discretion of the Investigator.
Chest X-Ray was not done for any patient participated in this study; ECG, electrocardiogram

Supplementary table 1: Schedule of study visits and assessment.

Study objectives

The primary objective was:

- To assess the relative bioavailability of two dosages of teneligliptin over a 24-hour interval at a steady state (measured by the area under curve, $AUC_{0–24ss}$).
- Secondary objectives were:
- To Measure maximum plasma concentration over a 12- or 24-h period at steady state ($C_{max,ss}$);
- To measure time to reach maximum concentration at steady state ($T_{max,ss}$);
- To measure peak to trough ratio at steady state for the 12- and 24-hour regimens estimated at steady state;
- To measure steady state based on pre-dose levels on Day 5, 6, and 7 for both treatment groups;
- To assess PD profile of teneligliptin which included AUC of DPP-4 inhibition curve ($AUC_{DPP4inh}$), peak DPP-4 inhibition (I_{max}), time to reach I_{max} (T_{Imax}), trough level inhibition at steady state (I_{trough}) as well as average inhibition effect over the dosing period ($AUC_{DPP4inh}$/dosing interval).
- Safety parameters (vital signs, physical examination, blood glucose level monitoring, clinical laboratory parameters, and ECG) were assessed at specified intervals throughout the study. The AEs were monitored throughout the study.

Statistical analysis

Sample size estimation was based on the assumptions that the Treatment/Reference ratio was 90-110% with an intra-subject variability set at approximately 15% at a significance level of 5% to provide a power of approximately 80% and bioequivalence limits of 80-125% (C_{max} and AUC_{0-t}).

A sample size of 22 subjects was considered sufficient to establish bioequivalence between the two teneligliptin formulations under fasting conditions with adequate power. The PK/PD parameters were calculated from the individual concentration data of the subjects who had completed the study. Non-compartmental analysis methods were used to estimate PK parameters for teneligliptin. Any missing values were not considered for the estimation of PK parameters. The log-transformed PK parameters were subjected to Analysis of Variance (ANOVA). Data collected during the study were analyzed using Phoenix® WinNonlin 8.1, and statistical analysis was performed using the statistical package SAS® 9.4.

The inhibition of DPP-4 activity (compared to baseline) was expressed as a percentage. The area under the DPP-4 inhibition-time curve for the dosing interval was calculated using the linear trapezoidal approximation method. Maximum DPP-4 inhibition (I_{max}) and the time to reach I_{max} were estimated directly from the observed values. The time required to inhibit 80% of DPP-4 was expressed graphically. The relationship between the degree of DPP-4 inhibition and the plasma concentrations of teneligliptin was evaluated by building a sigmoid I_{max} model. The 90% confidence intervals for AUC_{0-24ss} formed the basis for concluding the equivalence of test and reference product.

Results

Of the 84 subjects screened, 28 healthy male subjects were enrolled in the study (Figure 1). The mean (standard deviation: SD) age, height, weight, and BMI were 23.35 (2.85) years, 1.67 (0.06) m, 65.39 (8.40) kg, and 31.46 (5.41) kg/m^2, respectively. None of the subjects had any relevant or significant previous medical history that could affect the study results. All the enrolled subjects completed the study and were considered for PK and bioequivalence analysis.

Pharmacokinetics

The mean plasma concentration-time profiles of teneligliptin for both dosage regimens are shown in Figure 2. Comparison of geometric least-square (LS) means and $AUC_{0–24ss}$ values of teneligliptin 20 mg q.d. and 10 mg b.i.d. are shown in Table 2**.** Results show that 90% CI for AUC_{0-24ss} was within the bioequivalence criteria 80–125% for teneligliptin. The geometric mean $AUC_{0–24ss}$ with the 10 mg b.i.d. and 20 mg q.d. dosage regimen was 1944.91 ng·h/mL and 1958.71 ng·h/mL with a coefficient of variance of 14.71% and 15.06%, respectively **(**Table 3). The median time from dose to maximum concentration ($T_{max,ss}$) was 14 hours with teneligliptin 10 mg b.i.d. and 2 hours with the 20 mg q.d. dose. Other steady-state PK parameters were comparable, except for C_{max}, which was lower for teneligliptin 10 mg b.i.d. (as expected for a b.i.d. regimen) **(**Table 3**)**.

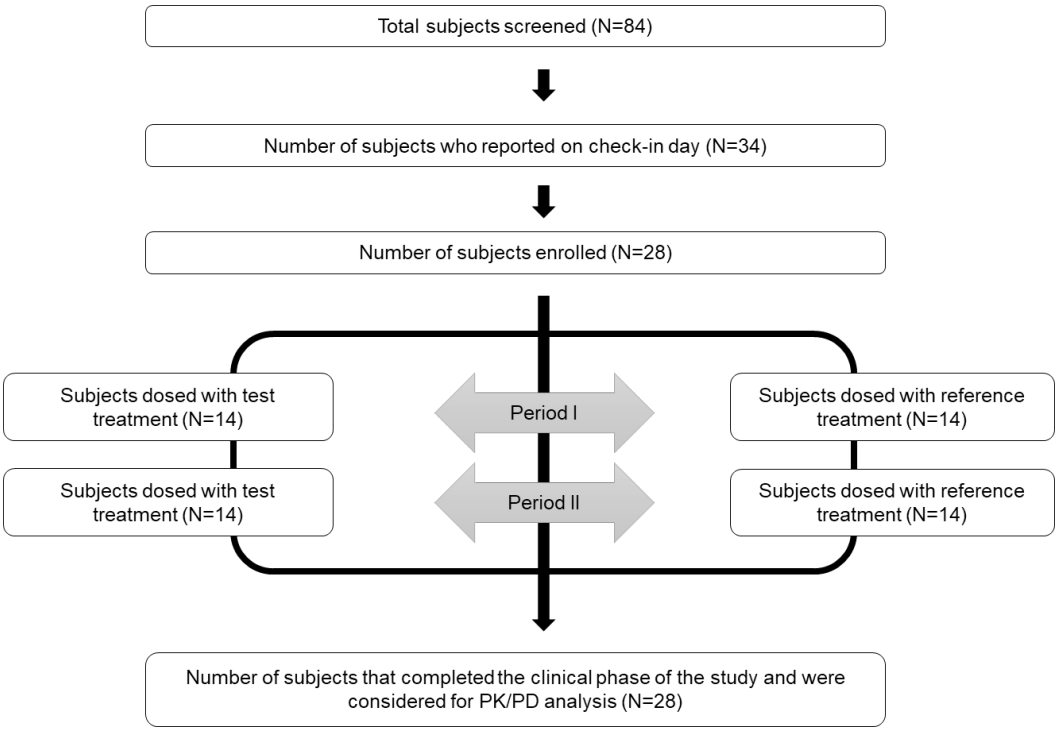

Figure 1: Study disposition flowchart [N, number of subjects; PK, pharmacokinetic; PD, pharmacodynamic; Reference, teneligliptin 20 mg once-daily; Test, teneligliptin 10 mg twice-daily].

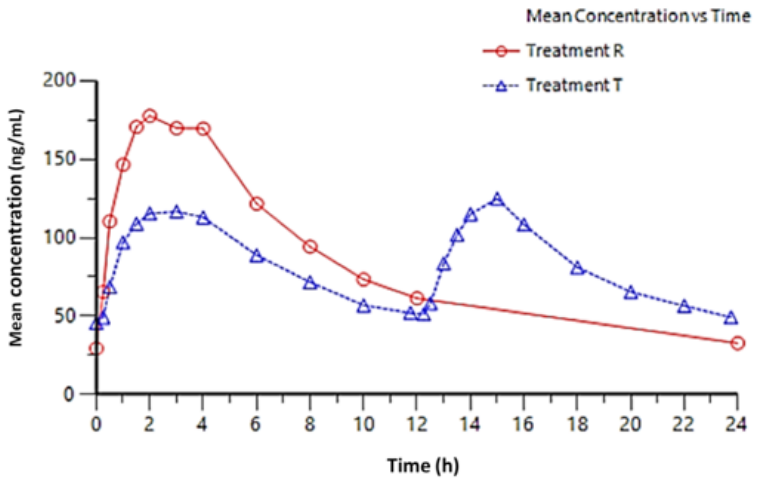

Figure 2: Mean plasma concentration (ng/mL) of teneligliptin versus Time (hour) plot for Reference and Test formulations [mL: Milliliter; ng: Nanogram; Reference (R), Teneligliptin 20 mg once-daily; Test (T), teneligliptin 10 mg twice-daily].

Teneligliptin						
Geometric Least Squares Mean (N=28)				90% Confidence Interval	Intra-Subject Variability CV (%)	Power (%)
PK Parameter	Test (T)	Reference (R)	% Ratio (T/R)			
$AUC_{0\text{-}24ss}$ (ng*hr/mL)	1944.91	1958.71	99.30	95.89 - 102.82	7.66	100.00
AUC: Area Under The Curve; CV: Coefficient of Variance; hr, Hour; mL: milliliter; ng: nanogram; N: Number of Evaluable Subjects; PK: Pharmacokinetic; Reference, teneligliptin 20 mg once-daily; SD, standard deviation; Test, teneligliptin 10 mg twice-daily						

Table 2: Bioequivalence summary of teneligliptin.

Teneligliptin 10 mg b.i.d.						
	C_{maxss} (ng/mL)	T_{maxss} (hr)	C_{minss} (ng/mL)	$AUC_{0\text{-}24ss}$ (ng*hr/mL)	C_{avss} (ng/mL)	C_{trough} (ng/mL)
N	28	28	28	28	28	28
Mean (SD)	139.49 (24.05)	10.91 (5.76)	43.68 (8.58)	1965.89 (289.11)	81.91 (12.05)	46.94 (9.013)
Median (Minimum–Maximum)	138.34 (103.64–217.65)	14 (0.50–15.00)	43.44 (27.61–64.76)	1976.27 (1436.03–2643.03)	82.34 (59.84–110.12)	46.79 (29.93–63.58)
CV%	17.24	52.83	19.66	14.71	14.71	19.2
Geometric mean	137.66	7.76	42.84	1944.91	81.04	46.09
Teneligliptin 20 mg q.d.						

N	28	28	28	28	28	28
Mean (SD)	215.09 (87.04)	2.47 (1.24)	28.67 (8.79)	1981.01 (298.34)	82.54 (12.43)	32.74 (8.66)
Median (Minimum–Maximum)	198.94 (133.83–587.28)	2.00 (0.25–4.00)	27.41 (14.86–52.48)	1953.24 (1401.52–2572.97)	81.38(58.39–107.21)	31.42(18.58–52.14)
CV%	40.47	50.00	30.68	15.06	15.06	26.45
Geometric mean	204.7	2.03	27.46	1958.71	81.61	31.66

AUC 0–24, ss, area under the plasma concentration-time curve from time zero to time 24.00 hours steady state; b.i.d., twice daily; CV, coefficient of variance; Cmaxss, maximum (peak) steady-state plasma drug concentration during a dosage interval; Cminss, minimum steady-state plasma drug concentration; Ctrough, trough plasma concentration (measured concentration at the end of a dosing interval at steady state [taken directly before next administration]); Cavss, average steady-state plasma drug concentration during multiple-dose administration; hr, hour; mL, milliliter; ng, nanogram; N, number of subjects; q.d., once daily; SD, standard deviation; Tmaxss, time to reach maximum (peak) plasma concentration following drug administration at steady state,

Table 3: Summary of pharmacokinetic parameters.

Pharmacodynamics

The mean DPP-4 inhibitor time profiles of teneligliptin for both dosage regimens are shown in Figure 3**.** The PD parameters of DPP-4 inhibitors are summarized in Table 4. Based on the PD data obtained, both dosage regimens tested (teneligliptin 10 mg b.i.d. and 20 mg q.d.) were approximately similar for $AUC_{DPP\text{-}4inh\ 0\text{-}12}$ and $AUC_{DPP\text{-}4inh\ 0\text{-}24}$. The maximal inhibition (I_{max}) for the reference (teneligliptin 20 mg q.d.) was numerically higher (89.0% vs. 85.4%) and could be attributed to the higher peak levels achieved with the 20 mg dose and a correspondingly higher plasma DPP-4 inhibition. The difference in I_{max} was statistically significant. A numerically higher trough inhibition (I_{trough}) was observed for the test (teneligliptin 10 mg b.i.d.) vs. the reference (teneligliptin 20 mg q.d.) (69.1% vs. 59.4%) treatment.

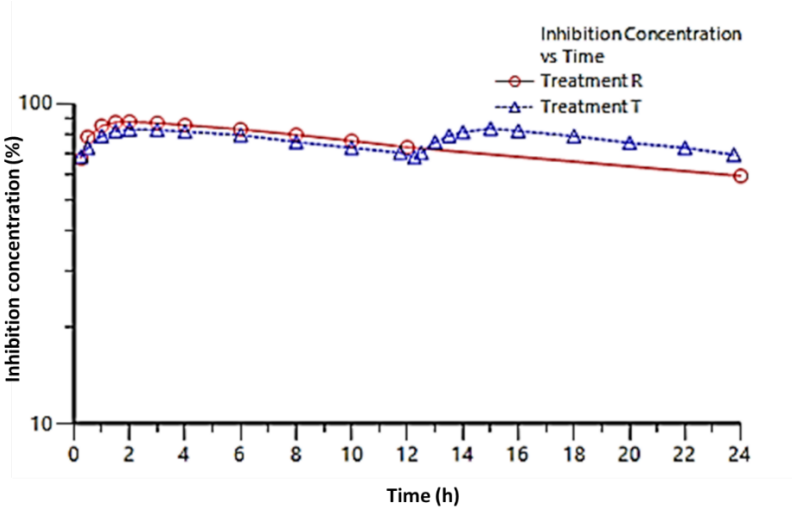

Figure 3: Mean DPP-4 inhibitor concentration (%) versus time (hour) plot for Reference and Test formulations [Reference (R), teneligliptin 20 mg once-daily; Test (T), teneligliptin 10 mg twice-daily].

Treatment	PD parameters	Mean (SD)	Median (Minimum–Maximum)	CV (%)	GM
Test	I_{max} (%)	85.46 (7.02)	86.11 (53.58–92.85)	8.21	85.12
	I_{min} (%)	65.27 (11.42)	67.59 (19.91–78.43)	17.50	63.72
	T_{Imax} (hr)	7.29 (6.29)	3.00 (0.50–16.00)	86.27	4.39
	$AUC_{DPP-4inh0-12}$	927.87 (109.20)	939.28 (474.32–1064.06)	11.77	919.60
	$AUC_{DPP-4inh0-24}$	1848.65 (223.77)	1876.65 (916.23–2116.24)	12.10	1830.96
	I_{trough}	69.11 (12.88)	72.18 (17.89–87.96)	18.64	67.15
	$AUC_{DPP-4inh/Dosing\ interval}$	77.03 (9.32)	78.19 (38.18–88.18)	12.10	76.29
Reference	I_{max} (%)	89.03 (3.34)	89.19 (79.60–94.68)	3.75	88.97
	I_{min} (%)	58.74 (15.18)	61.01 (0.00–80.45)	25.85	--
	T_{Imax} (hr)	2.33 (1.62)	2.00 (0.25–8.00)	69.34	1.87
	$AUC_{DPP-4inh0-12}$	973.64 (95.40)	984.70 (551.07–1071.95)	9.80	967.73
	$AUC_{DPP-4inh0-24}$	1768.22 (249.07)	1800.59 (716.65–2091.19)	14.09	1743.23
	I_{trough}	59.38 (15.55)	61.04 (0.00–84.09)	26.18	--
	$AUC_{DPP-4inh/Dosing\ interval}$	73.68 (10.38)	75.02 (29.86–87.13)	14.09	72.63

AUCDPP-4inh0-12, area under the curve of DPP-4 inhibition over 12 hours period at steady state; AUCDPP-4inh0-24, area under the curve of DPP-4 inhibition over 24 hours period at steady state; AUCDPP-4inh/dosing interval, average DPP-4 inhibition overdosing period; DPP-4inh, dipeptidyl peptidase-4 inhibition; CV, coefficient of variance; GM, geometric mean; hr, hour; Imax, maximum DPP-4 inhibition; Imin, minimum DPP-4 inhibition; Itrough, trough level inhibition at steady state; PD, pharmacodynamic; Reference, teneligliptin 20 mg once-daily; SD, standard deviation; TImax, time to reach Imax; Test, teneligliptin 10 mg twice-daily

Table 4: Summary of pharmacodynamic parameters for teneligliptin on un-transformed data under fasting conditions (DPP-4 inhibitor).

Safety

No AEs were reported during the study. There was no abnormality observed in vital signs, physical findings, and blood glucose levels for any subjects. The laboratory parameters were well within the clinically specified range at the end of the study. No patient had withdrawn from the study due to safety-related concerns.

Discussion

Diabetes prevalence rose from 422 million in 2014 to 537 million in 2021 and is expected to rise to 643 million by 2030. [2,22] In line with the dosage regimen of most commonly administered antidiabetic medications such as metformin and to manage treatment compliance, a twice daily dosage regimen of teneligliptin is required. In most clinical trials, teneligliptin has been studied as a single dose regimen (teneligliptin 20 mg q.d.) [14,16]. To establish that twice daily regimen of teneligliptin would have similar bioavailability to single daily dose, our study compared the steady state PK/PD of the two regimens in healthy adult subjects.

In our study, we found that both the regimens were equivalent in terms of absorption rate during the 24-h period for the test and reference formulation of teneligliptin (Ratio of the LS mean: 99.30%) demonstrating comparable PK profile with low intra-subject variability. Similar absorption rate during the 24-h period were observed in a 4-week study conducted by Eto, et al., median time to maximum concentration (C_{max}) of 1.0 hour in both groups and a mean $t_{1/2}$ of 20.8 and 18.9 hours in both teneligliptin 10 and 20 mg q.d., respectively. [6] An essential PD parameter to establish efficacy for any DPP-4 inhibitor is the extent of DPP-4 inhibition. In our study, both dosage regimens resulted in a similar and sufficient DPP-4 inhibition over the whole dosing interval, indicating comparable efficacy. Similar results concerning DPP-4 inhibition have also been observed in a 4-week study conducted by Eto, et al., the percentage of DPP-4 inhibition was 81.3% and 89.7%, 2-hour after administration of teneligliptin 10 and 20 mg q.d., respectively [6].

Teneligliptin is generally well-tolerated in subjects with T2DM when used as monotherapy or add-on therapy to other antidiabetic drugs such as metformin, glimepiride, and pioglitazone [9,11,12,14,18]. In a study investigating teneligliptin as a monotherapy, the most commonly reported AEs were nasopharyngitis, a positive urine ketone body, urine glucose, and urinary protein [10]. In our study, no safety findings were reported, and both teneligliptin regimens were well tolerated.

The strength of our study was that it was a two-way crossover study design that is implicated to be the best option to test the relative bioavailability of drugs as each participant serves as their control, thereby eliminating inter-subject and intra-subject variability from the comparison. A washout phase was not required in our study because the same daily dose of teneligliptin was used in each treatment period. In addition, both treatments were at a steady state at the point of crossover between treatments.

However, our study was limited by short duration that do not allow evaluation of therapeutic efficacy of the treatment regimens. However, the objective of bioequivalence studies is not to evaluate of therapeutic efficacy.

Overall, the current study suggests that teneligliptin 20 mg q.d. has effective DPP-4 inhibition and change in regimen from 20 mg q.d. to 10 mg b.i.d. is expected to demonstrate similar DPP-4 inhibition and, thereby, glycemic control. Additionally, the twice daily regimen, is expected to make FDC possible with antidiabetic drugs with similar dosing regimen which in turn make the dosing regimen convenient for subjects with improved medication adherence.

Conclusion

Teneligliptin 10 mg b.i.d. found to be bioequivalent to a 20 mg q.d. regimen, with comparable DPP-4 inhibition, and well tolerated at both dosages in this crossover study.

References

1. Pradeepa R, Mohan V (2017) Prevalence of type 2 diabetes and its complications in India and economic costs to the nation. Eur J Clin Nutr 71(7): 816-824.
2. International Diabetes Federation. Diabetes Atlas (2021).
3. Takamiya Y, Okamura K, Shirai K, Okuda T, Kobayashi K, et al. (2020) Multicenter prospective observational study of teneligliptin, a selective dipeptidyl peptidase-4 inhibitor, in patients with poorly controlled type 2 diabetes: Focus on glycemic control, hypotensive effect, and safety Chikushi Anti-Diabetes Mellitus Trial-Teneligliptin (CHAT-T). Clin Exp Hypertens 42(3): 197-204.
4. Kim HJ, Kim YS, Lee CB, Choi MG, Chang HJ, et al. (2019) Efficacy and Safety of Switching to Teneligliptin in Patients with Type 2 Diabetes Inadequately Controlled with Dipeptidyl Peptidase-4 Inhibitors: A 12-Week Interim Report. Diabetes Ther 10(4): 1271-1282.
5. Chen XW, He ZX, Zhou ZW, Yang T, Zhang X, et al. (2015) Clinical pharmacology of dipeptidyl peptidase 4 inhibitors indicated for the treatment of type 2 diabetes mellitus. Clin Exp Pharmacol Physiol 42(10): 999-1024.
6. Eto T, Inoue S, Kadowaki T (2012) Effects of once-daily teneligliptin on 24-h blood glucose control and safety in Japanese patients with type 2 diabetes mellitus: A 4-week, randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab 14: 1040–1046.
7. Kishimoto M (2013) Teneligliptin: a DPP-4 inhibitor for the treatment of type 2 diabetes. Diabetes Metab Syndr Obes 6: 187-195.
8. Nakamaru Y, Hayashi Y, Ikegawa R, Kinoshita S, Perez Madera B, et al. (2014) Metabolism and disposition of the dipeptidyl peptidase IV inhibitor teneligliptin in humans. Xenobiotica 44(3): 242-253.
9. Kadowaki T, Kondo K (2014) Efficacy and safety of teneligliptin added to glimepiride in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled study with an open-label, long-term extension. Diabetes Obes Metab 16(5): 418-425.
10. Kadowaki T, Kondo K (2013) Efficacy, safety and dose-response relationship of teneligliptin, a dipeptidyl peptidase-4 inhibitor, in Japanese patients with type 2 diabetes mellitus. Diabetes Obes Metab 15(9) :810-818.
11. Kadowaki T, Kondo K (2013) Efficacy and safety of teneligliptin in combination with pioglitazone in Japanese patients with type 2 diabetes mellitus. J Diabetes Investig 4: 576–584.
12. Kim MK, Rhee EJ, Han KA, Woo AC, Lee MK, et al. (2015) Efficacy and safety of teneligliptin, a dipeptidyl peptidase-4 inhibitor, combined with metformin in Korean patients with type 2 diabetes mellitus: a 16-week, randomized, double blind, placebo-controlled phase III trial. Diabetes Obes Metab 17(3): 309–312.
13. Tanaka S, Suzuki K, Aoki C, Niitani M, Kato K, et al. (2014) Add-on treatment with teneligliptin ameliorates glucose fluctuations and improves glycemic control index in Japanese patients with type 2 diabetes on insulin therapy. Diabetes Technol Ther 16(12): 840–845.
14. Ji L, Li L, Ma J, Li X, Li D, et al. (2021) Efficacy and safety of teneligliptin added to metformin in Chinese patients with type 2 diabetes mellitus inadequately controlled with metformin: A phase 3, randomized, double-blind, placebo-controlled study. Endocrinol Diabetes Metab 20; 4(2): e00222.
15. Noda T, Ebihara E, Ueno H, Sadohara K, Tanaka Y, et al. (2019) Concurrent Use of Teneligliptin and Canagliflozin Improves Glycemic Control with Beneficial Effects on Plasma Glucagon and Glucagon-Like Peptide-1: A Single-Arm Study. Diabetes Ther 10(5): 1835-1846.
16. Ji L, Ma J, Lu W, Liu J, Zeng J, et al. (2021) Phase III, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of teneligliptin monotherapy in Chinese patients with type 2 diabetes mellitus inadequately controlled with diet and exercise. J Diabetes Investig 12(4): 537-545.
17. Nakamaru Y, Hayashi Y, Davies M, Jürgen Heuer H, Hisanaga N, et al. (2015) Investigation of Potential Pharmacokinetic Interactions Between Teneligliptin and Metformin in Steady-state Conditions in Healthy Adults. Clin Ther 37(9): 2007-2018.
18. Patnaik SR (2018) Efficacy and Safety of Addition of Teneligliptin to Type 2 Diabetes Patients Inadequately Controlled with Triple Drug Treatment with Glimepride + metformin + Voglibose. Journal of Medical Science And clinical Research 6(3): 92-97.
19. Chudasama D, Saboo B, Panchal D, Patel F, Saiyed M, et al. (2018) The Efficacy of Teneligliptin with Metformin in Drug-Naïve Type 2 Subjects. Diabetes 67: 1205-P.
20. Schwartz S, Fonseca V, Berner B, Cramer M, Chiang YK, et al. (2006) Efficacy, tolerability and safety of a novel once-daily extended-release metformin in patients with type 2 diabetes. Diabetes Care 29: 759–764.
21. Ahrén B (2008) Novel combination treatment of type 2 diabetes DPP-4 inhibition + metformin. Vasc Health Risk Manag 4(2): 383-394.
22. (2022) Diabetes. World Health Organization.