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Contents

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INTRODUCTION

Teneligliptin: Binding modes in the active site of DPP-4

Dipeptidyl peptidase IV inhibitors are a class of oral anti-hyperglycemic agents for the treatment of type 2 diabetes. The anti-glycemic effect of DPP-4 inhibitors is mediated by inhibiting the degradation of the incretin hormone glucagon-like peptide-1 (GLP-1) and stimulating insulin release in response to increased blood glucose levels. Among all DPP-4 inhibitors, vildagliptin, saxagliptin and teneligliptin are peptide mimetic compounds, which have been discovered by replacing segments of peptide-based substrates. Whereas, sitagliptin, alogliptin and linagliptin are non-peptide mimetic compounds, which have been discovered by optimization of the initial lead compounds identified by random screening. Therefore, their chemical structures are diverse, suggesting that each of their binding modes in DPP-4 would be unique.

On the basis of binding subsites all DPP4 inhibitors are categorized into 3 classes (Table 1 and Figure 1).

Table 1. Three classes of DPP4 inhibitors

Class	Criteria	Molecules
I	Binding to S_1 & S_2 only (interactions with the core S_1 and S_2 subsites and a covalent bond with Ser630 in the catalytic triad)	Saxagliptin Vildagliptin
II	Binding to S_1, S_2 & S'_1, S'_2 (interactions with the S'_1 and/ or S'_2 subsites in addition to the S_1 and S_2 subsites;)	Linagliptin Alogliptin
III	Binding to S_1, S_2 & S_2 extensive subsites (interactions with the S_1, S_2 and S_2 extensive subsites)	Sitagliptin Teneligliptin

The triazolopyrazine moiety and trifluoromethyl substituent of sitagliptin and the piperazine moiety, of teneligliptin bind to the S_2 extensive subsite. Although both inhibitors appear to bind to the subsites in the same manner, teneligliptin has 5-fold higher activity. Following three potential reasons may be responsible for the difference.

- Teneligliptin consists of a considerably rigid "J-shaped" structure formed by five rings, four of which are directly connected, the loss in entropy is small upon binding to DPP-4.
- The carbonyl group of teneligliptin, derived from the peptide mimetics, forms a hydrogen bond with the side chain of Asn710.
- for teneligliptin, introduction of the "anchor lock domain", which binds to the S_2 extensive subsite, increased the activity by 1500-fold over the corresponding fragment that binds to S_1 and S_2 only.

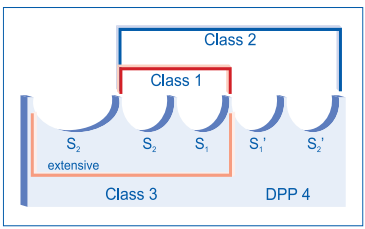


Figure 1. The concept of 3 classes on the basis of the inhibitor's binding subsites

Because of above mentioned unique features teneligliptin is one of the most potent DPP4 inhibitor (Table 2)

Table 2. The DPP-4 inhibitory activity

Compound	DPP-4 inhibition, IC50 (nmol/L)
Vildagliptin	29.2
Saxagliptin	6.3
Alogliptin	4.9
Linagliptin	0.6
Sitagliptin	10.3
Teneligliptin	1.9

CLINICAL PARTICULARS

Therapeutic indications

Teneligliptin Tablets are indicated as a monotherapy adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

Contraindications

Teneligliptin Tablets are contraindicated in patients with:

- Hypersensitivity to the drug or any of its components
- Severe ketosis, diabetic coma or pre-coma and also for immediate remedy in type 1 diabetes
- Severe trauma, before and after surgery and when the blood glucose has to be controlled with insulin injection.

Interaction with other medicinal products and other forms of interaction

This product was metabolized mainly by CYP3A4 and flavin-containing monooxygenases (FMO1 and FMO3), and urinary excretion rate of unaltered substance was 14.8% to 22.1%.

Glimepiride combination:

When a repeated dose of 1 mg glimepiride for four days and a single combined dose (2nd day of glimepiride administration) of 40 mg teneligliptin were administered to the healthy adults, the ratio (90% confidence interval [CI]) of C_{max} of teneligliptin and $AUC_{0-\infty}$ geometric mean value was 0.971 (0.866- 1.088) and 0.926 (0.894 – 0.959) with respect to single-dose administration of teneligliptin alone. Furthermore, when a repeated-dose of 40 mg teneligliptin for seven days and a single combined

Table 3. Precautions for co-administration of teneligliptin tablets with other drugs

Drug name	Clinical condition/ Measures	Mechanism / risk factors
Drugs for diabetes Sulfonylurea fast-acting insulin secretagogue α-glucosidase inhibitor Biguanide Thiazolidinediones GLP-1 analog preparation SGLT2 inhibitor Insulin preparation	Since hypoglycemia might occur, these drugs should be administered while carefully observing the patient's condition. Particularly, when co administered with sulfonylurea or insulin formulation, there is a possibility of higher risk of hypoglycemia. In order to reduce the risk of hypoglycemia caused by sulfonylurea or insulin formulation, consider decreasing the quantity of sulfonylurea or insulin formulation. When hypoglycemia is observed, usually, cane sugar should be given, and when co-administered with α-glucosidase inhibitor, glucose should be given.	Hypoglycemic action is increased.
Drugs increasing hypoglycemic action β-blocking agents Salicylic acid Monoamine oxidase inhibitor	Since the blood sugar may further decrease, these drugs should be administered while carefully observing the patient's condition in addition to blood sugar level.	Hypoglycemic action is increased.
Drugs decreasing hypoglycemic action Adrenalin adrenocortical hormone	Since the blood sugar may increase, these drugs should be administered while carefully observing the patient's condition in addition to blood sugar level.	Hypoglycemic action is decreased.
Thyroid hormone		
Drugs known to cause QT prolongation **Class IA antiarrhythmic drug** Quinidine sulfate hydrate, procainamide hydrochloride **Class III antiarrhythmic drugs** amiodarone hydrochloride, sotalol hydrochloride	QT prolongation might occur.	QT prolongation is seen with single administration of these drugs.

dose (7th day of teneligliptin administration) of 1 mg glimepiride were administered to the healthy adults, the ratio (90% CI) of C_{max} of glimepiride and $AUC_{0-\infty}$ geometric mean value was 1.016 (0.932 – 1.106) and 1.023 (0.978 – 1.071) with respect to single-dose administration of glimepiride alone.

Pioglitazone combination:

When a repeated dose of 30 mg pioglitazone for nine days and a single combined dose (7th day of pioglitazone administration) of 40 mg teneligliptin were administered to the healthy adults, the ratio (90% CI) of C_{max} of teneligliptin and $AUC_{0-\infty}$ geometric mean value was 1.117 (0.984 -1.266) and 1.005 (0.967 - 1.045) with respect to single-dose administration of teneligliptin alone, and the C_{max} of teneligliptin increased 11.7% due to co-administration. Furthermore, when a repeated-dose of 40 mg teneligliptin for nine days and a single combined dose (7th day of teneligliptin administration) of 30 mg pioglitazone were administered to the healthy adults, the ratio (90% CI) of C_{max} of pioglitazone and $AUC_{0-\infty}$ geometric mean value was 1.004 (0.917 - 1.100) and 1.134 (1.060 - 1.213) with respect to single-dose administration of pioglitazone alone. Similarly, the ratio (90% CI) of C_{max} of active metabolites (M-III and M-IV) of pioglitazone and $AUC_{0-\infty}$ geometric mean value was 1.041 (0.975 - 1.113) and 1.116 (1.056 - 1.180) in M-III and 1.028 (0.963 - 1.096) and 1.088 (1.032 - 1.147) in M-IV.

Metformin combination:

When a repeated dose of 40 mg teneligliptin once daily for eight days and a repeated combined dose (6 to 8th day of teneligliptin administration) of 850 mg metformin twice daily were administered to the healthy adults, the ratio (90% CI) of C_{max} of teneligliptin and AUC_{0-24} hr geometric minimum mean-square value was 0.907 (0.853 - 0.965) and 1.042 (0.997 - 1.089) with respect to repeated-dose administration of teneligliptin only. Furthermore, when a repeated combined dose (4th to 8th day of metformin administration) of 850 mg metformin twice daily for eight days and 40 mg teneligliptin once daily was administered to the healthy adults, the ratio (90% CI) of C_{max} of metformin and AUC_{0-12} hr geometric minimum mean-square value was 1.057 (0.974 - 1.148) and 1.209 (1.143 - 1.278) with respect to repeated-dose administration of metformin only, and the AUC_0-12 hr of metformin increased to 20.9% due to co-administration.

Ketoconazole combination:

When a repeated dose of 400 mg ketoconazole for six days and a single combined dose (4th day of ketoconazole administration) of 20 mg teneligliptin were administered to the healthy adults, the ratio (90% CI) of C_{max} of teneligliptin and $AUC_{0-\infty}$ geometric minimum mean-square value was 1.37 (1.25 - 1.50) and 1.49 (1.39 - 1.60) with respect to single-dose administration of teneligliptin alone, and it increased to 37% and 49% due to co-administration.

Pregnancy and lactation

Teneligliptin should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. (The safety of this product in pregnant women has not been established. Furthermore, the transfer to embryo in animal studies (rats) has been reported.)

Breast-feeding must be discontinued during administration of this product in lactating women (transfer to milk in animal studies (rats) has been reported.).

Undesirable effects

The following adverse drug reactions have been identified in the clinical trials on Teneligliptin.

In clinical trials conducted in Japan, 232 adverse reactions to this drug (including abnormal laboratory tests) were reported in 156 patients (9.5%) of total 1645 patients. The most frequently observed adverse reactions were hypoglycemia in 43 patients (2.6%) and constipation in 14 patients (0.9%).

Patients with Inadequate Glycemic Control on Diet and Exercise Alone

In a clinical study conducted in 237 Indian patients with Type 2 Diabetes Mellitus inadequately controlled on diet and exercise alone, a total of 158 patients were exposed to Teneligliptin Tablets

for a mean duration of 106.7 days. Adverse events considered to be related to study medication were reported for 6/158 (3.8%) of patients in the Teneligliptin group.

The most frequent individual adverse event was dizziness in Teneligliptin group (5/158) 3.2%, followed by headache in (5/158) 3.2%, diarrhea in (4/158) 2.5% and pyrexia in (4/158) 2.5%. An AE (cancer right pyriform fossa) leading to early termination from the study was reported for 1/158(0.6%) of patients in the Teneligliptin group, this was unrelated to the study drug. No SAE related to the study drug was reported during the study. Most of the adverse events were mild in severity.

Significant adverse reactions:

a) Hypoglycemia
b) Intestinal Obstruction (0.1%)
c) Liver dysfunction (unknown frequency)
d) Interstitial pneumonia (frequency unknown)

Other adverse reactions/side effects:

If adverse reactions are observed, then the drug administration should be discontinued and appropriate measures should be taken.

Table 4. Other adverse reactions

Incidence/Types	0.1% ~ 1%	< 0.1%
Digestive system	Constipation, abdominal swelling, abdominal discomfort, nausea, stomach ache, flatulence, stomatitis, gastric polyp, colon polyp, duodenal ulcer, reflux esophagitis, diarrhea, anorexia, increased amylase, increased lipase, acute pancreatitis	
Liver	Increased AST (SGOT), increased ALT (SGPT), and increased γ-GTP	Rise in ALP
Kidney and urinary system	Albuminuria, positive ketone body in urine, increased uric acid in blood	
Skin	Eczema, Wet rash, pruritus, allergic dermatitis	
Others	Increased CK (CPK), increased serum potassium, fatigue, allergic rhinitis, and increased serum uric acid	

Overdose

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

CLINICAL PHARMACOLOGY

Mechanism of Action

The glucagon-like peptide-1 (GLP-1) is secreted from alimentary canal in response to meal that promotes insulin secretion from pancreas and regulates blood sugar post meal by controlling glucagon secretion. Teneligliptin exhibits a hypoglycemic effect by controlling the degradation of GLP-1 by inhibiting dipeptidyl peptidase-4 (DPP-4) activity and thereby increasing blood concentration of active GLP-1.

Pharmacodynamics

DPP-4 inhibitory action and GLP-1 degradation inhibitory action

1. Teneligliptin inhibits concentration-dependent human plasma DPP-4 activity, and its IC50 value (95% CI) was 1.75 (1.62 - 1.89) nmol/L (in vitro).
2. Teneligliptin concentration-dependently suppressed the degradation of GLP-1 in rat plasma, with IC50 values and its 95% CI being 2.92 nM [2.21, 3.87] (in vitro).
3. In the glucose tolerance test using Zucker Fatty rat, an obesity model showing insulin resistance and abnormal glucose tolerance, teneligliptin increased plasma active form GLP-1 concentration and plasma insulin concentration by its single-dose administration.

4. In patients having type 2 diabetes mellitus, the administration of 20 mg teneligliptin once daily inhibited the plasma DPP-4 activity and increased the plasma active form GLP-1 concentration.

Glucose tolerance improvement action

1. In the glucose tolerance test using Zucker Fatty rat, an obesity model showing insulin resistance and abnormal glucose tolerance, teneligliptin controlled an increase in the blood sugar level by its single-dose administration
2. In patients having type 2 diabetes mellitus, the administration of 20 mg teneligliptin once daily improved the blood sugar after breakfast, lunch, and dinner and the fasting blood sugar

Pharmacokinetics

Plasma concentration:

1. Single – dose administration:

   The plasma concentration changes and the pharmacokinetic parameters of teneligliptin after a single oral dose of 20 mg and 40 mg of teneligliptin given empty stomach to the healthy adults are shown below.

Table 5. Pharmacokinetic parameters at the time of single dose oral drug administration in healthy adults

Strengths	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng.hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)
20 mg	187.20 ± 44.70	2028.9 ± 459.5	1.8 (1.0-2.0)	24.2 ± 5.0
40 mg	382.40 ± 89.83	3705.0 ± 787.0	1.0 (0.5-3.0)	20.8 ± 3.2

n = 6, Mean Value ± SD, t_{max} = Central value (minimum value - maximum value)

2. Repeated – dose administration:

   The pharmacokinetic parameters of teneligliptin after a repeated dose of 20 mg of teneligliptin once daily for seven days given 30 minutes before breakfast to the healthy adults are shown below. The state of equilibrium will be attained within seven days.

Table 6. Pharmacokinetic parameters at the time of repeated dose oral drug administration in healthy adults

	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ hr (ng.hr/mL)	$AUC_{0\text{-}inf}$ (ng.hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)
After first dose	160.60 ± 47.26	1057.2 ± 283.9	1627.9 ± 427.8	1.0(0.4-2.0)	25.8 ± 4.9
7 days after administration	220.14 ± 59.86	1514.6 ± 370.5	2641.4 ± 594.7	1.0(1.0-1.0)	30.2 ± 6.9

n = 7, Mean Value ± SD, t_{max} = Central value (minimum value - maximum value)

3. Food effect:

   C_{max} decreased after a single dose of 20 mg of teneligliptin given post meal to the healthy adults as compared to empty stomach and t_{max} prolonged from 1.1 hr to 2.6 hr; however, no difference observed in AUC

Table 7. Pharmacokinetic parameters at the time of fasting and after food intake in healthy adults

	C_{max} (ng/mL)	$AUC_{0\text{-}72}$ hr (ng.hr/mL)	$AUC_{0\text{-}inf}$ (ng.hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)
Empty Stomach	232. 2 (236.2 ± 43.77)	1855.5 (1861.1 ± 148.1)	2090.3 (2094.6 ± 1 38.5)	1.1 ± 0.4 26.5	26.5 (27.8 ± 9.3)
Post Meal	184.9 (187.5 ± 33.55)	1806 (1814.6 ± 183.3)	2044.0 (2056.1 ± 230.9)	2.6 ± 1.1 26.9	26.9 (28.3 ± 9.5)

n = 14, Geometric mean (Arithmetic mean value ± Standard Deviation)

t_{max} = Arithmetic mean value ± Standard Deviation

Rate of protein binding:

The protein binding ratio was 77.6% to 82.2% when the [^{14}C] label teneligliptin (20, 100, and 500 ng/mL) was added to the human plasma (in vitro)

Metabolism:

1. Following a single oral administration of 20 mg [^{14}C] label teneligliptin to the healthy adults, the unaltered substance and the metabolites M1, M2, M3, M4, and M5 were observed in the blood plasma. Furthermore, the ratio of $AUC_{0-\infty}$ of teneligliptin, M1, M2, M3, M4, and M5 with respect to $AUC_{0-\infty}$ calculated from the plasma radioactive concentration up to 72 hours after administration was 71.1%, 14.7%, 1.3%, 1.3%, 0.3%, and 1.1%.
2. Mainly, CYP3A4 and flavin-containing monooxygenases (FMO1 and FMO3) participate in the metabolism of teneligliptin. Furthermore, although it showed a weak inhibitory action towards CYP2D6, CYP3A4, and FMO (IC50 value: 489.4, 197.5, and 467.2μmol/L), it did not showed inhibitory action towards CYP1A2, CYP2A6,CYP2B6, CYP2C8, CYP2C8/9, CYP2C19, and CYP2E1, and CY P1A2 and CYP3A4 were not introduced (in vitro).

Excretion:

1. When a single oral dose of 20 mg and 40 mg teneligliptin was given to the healthy adults on empty stomach, about 21.0 to 22.1% of dose was excreted as unaltered substance in urine, and the renal clearance was 37 to 39 mL/hr/kg.
2. When a single oral dose of 20 mg [^{14}C] label teneligliptin was given to the healthy adults, 45.4% of dosage radioactivity was excreted in urine and 46.5% was excreted in faeces up to 216 hours after administration. Furthermore, with respect to the dosage up to 120 hours after administration, the accumulated urinary excretion rate of unaltered substance, M1,M2, and M3 was 14.8%, 17.7%, 1.4%, and 1.9%, respectively and the accumulated faeces excretion rate of unaltered substance, M1, M3, M4, and M5 was 26.1%, 4.0%, 1.6%,0.3%, and 1.3%, respectively.
3. Teneligliptin is a substrate of P-glycoprotein that inhibited the transportation of digoxin up to 42.5% through P-glycoprotein in the concentration of 99μmol/L. Furthermore, it showed a weak inhibitory action towards the organic anion transporter OAT 3 appeared in kidney, (IC50 value: 99.2μmol/L); however, it did not showed inhibitory action towards OAT 1 and organic cation transporter OCT2 (in vitro).

Renal dysfunction:

When a single oral dose of 20 mg teneligliptin was given to the renal dysfunction patients, no remarkable change was observed in C_{max} and t1/2 depending on the extent/degree of renal dysfunction. On the other hand, in the mild renal dysfunction patient (Ccr $\geq$ 50 to $\leq$ 80mL/min), moderate renal dysfunction patient (Ccr $\geq$ 30 to $\leq$ 50mL/min), and severe renal dysfunction patient (Ccr $<$ 30mL/min), the $AUC_{0-\infty}$ was found to be about 1.25 times, 1.68 times, and 1.49 times, respectively, as compared to the healthy adults, and AUC_{0-43h_r} of terminal renal failure affected individual was about 1.16 times as compared to the healthy adults. Furthermore, 15.6% of teneligliptin dose was removed due to haemodialysis.

Liver dysfunction:

When a single oral dose of 20 mg teneligliptin was given to the hepatic dysfunction patients, the C_{max} of teneligliptin was found to be about 1.25 times and 1.38 times and $AUC_{0-\infty}$ was about 1.46 times and 1.59 times, respectively, in slight hepatic dysfunction patient (total score 5 $\sim$ 6 by Child-Pugh classification) and moderate hepatic dysfunction patient (total score 7 $\sim$ 9 by Child-Pugh classification) as compared to the healthy adults. Note that there was no clinical experience in high degree hepatic dysfunction patient (total score more than 9 by Child-Pugh classification).

Pharmacokinetics in Elderly Patient

When a single oral dose of 20 mg teneligliptin was given to the healthy elderly patients ($\geq$ 65 years old $\leq$ 75 years old, 12 patients) and non-elderly patients ($\geq$ 45 years old $\leq$ 65 years old, 12 patents) on empty stomach, the ratio (90% CI) of geometric minimum mean-square value of elderly patient with C_{max}, $AUC_{0-\infty}$, and t1/2 of non-elderly patient was almost similar, 1.006 (0.871- 1.163) , 1.090 (0.975 - 1.218), and 1.054 (0.911- 1.219), respectively.

CLINICAL STUDIES

In patients with type 2 diabetes, treatment with teneligliptin produced clinically significant improvements in hemoglobin A1C, fasting plasma glucose (FPG) and 2-hour post-prandial glucose (PPG) compared to placebo.

Monotherapy

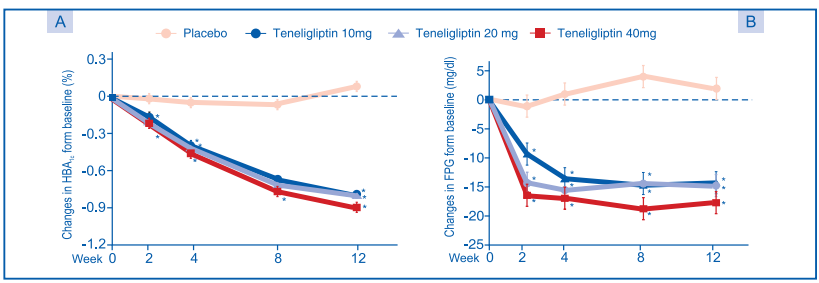
Placebo-controlled double blind comparative study of 12 weeks (Dose ranging study)

A total of 324 patients with type 2 diabetes participated in double-blind, placebo-controlled study to evaluate the efficacy and safety of teneligliptin monotherapy. The study consisted of a 4-week, single-blind, run-in phase in which patients received placebo, a 12-week, randomized, double blind treatment phase in which patients were treated with teneligliptin 10, 20 or 40 mg or placebo and a 2-week untreated observation phase.

Table 8. Glycemic Parameters in 12 Week Placebo-Controlled Study of Teneligliptin in Patients with Type 2 Diabetes (Dose ranging study)

Glycemic Parameters	Teneligliptin 10 mg	Teneligliptin 20 mg	Teneligliptin 40 mg	Placebo
A1C (%)	**N=84**	**N=84**	**N=81**	**N=80**
Baseline	7.9(0.7)	7.8(0.7)	7.7(0.7)	8.0
Change from baseline*	-0.8(0.1)	-0.8(0.1)	-0.9(0.1)	0.1(0.1)
Difference from placebo**	-0.9 (-1.0,-0.7)***	-0.9 (-1.1,-0.7)***	-1.0 (-1.2,-0.9)***	
Patients (%) achieving A1C $<$ 6.8%	32.5	40.5	51.3	2.6
Patients (%) achieving A1C $<$ 7.3%	56.5	66.1	79.7	12.7
FPG (mg/dL)	**N=84**	**N=84**	**N=81**	**N=80**
Baseline	148.0 (22.4)	143.0 (26.8)	141.9 (28.3)	150.0 (30.3)
Change from baseline*	-15.0 (2.0)	-14.1 (2.1)	-17.2 (2.0)	2.8 (2.0)
Difference from placebo**	-17.8 (-23.4,-12.1)***	-16.9 (-22.6,-11.2)***	-20.0 (-25.7,-14.3)***	
2-hour PPG (mg/dL)	**N=83**	**N=76**	**N=76**	**N=76**
Baseline	240.0 (55.5)	231.9 (53.6)	224.2 (54.8)	242.0 (46.7)
Change from baseline*	-43.3 (4.3)	-49.4 (4.5)	-51.3 (4.5)	7.3 (4.5)
Difference from placebo**	-50.6 (-62.8,-38.4)***	-56.8 (-69.2,-44.3)***	-58.6 (-71.1,-46.1)***	

* Values are means (s.d.), except least-squares means (s.e.), ** Values are means (s.d.), except least-squares means (95% confidence intervals), *** $p < 0.001$



* $p<0.001$

Figure 2. Changes in HbA1c (A) and fasting plasma glucose (B) from baseline to week 12.

Teneligliptin at 10, 20 and 40 mg daily provided significant improvements in HbA1C (hemoglobin A1C), FPG, and 2-hour PPG compared to placebo (See Table 8 and Figures 2, 3 and 4).

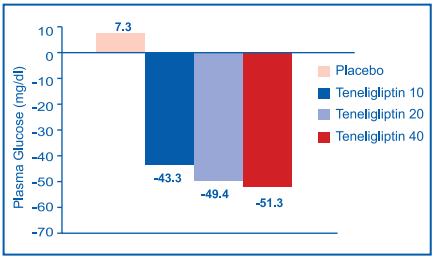


Figure 3. Changes in 2 h PPG from baseline to 12 weeks

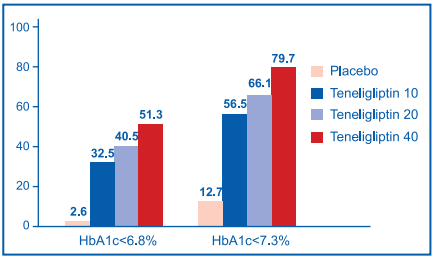


Figure 4. % of patients achieving HbA1c of 6.8% & 7.3%

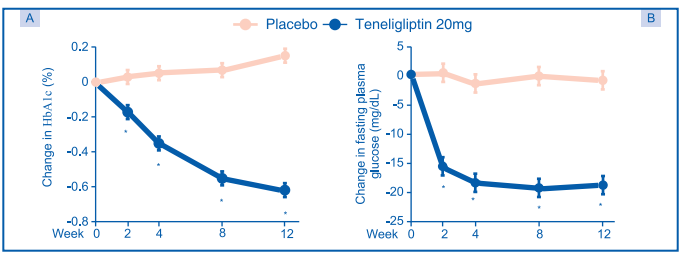
Placebo-controlled double blind comparative study of 12 weeks (Confirmatory study)

20 mg of teneligliptin or placebo once daily for 12 weeks was administered to the patients (203) having type 2 diabetes mellitus where glycemic control by diet and exercise therapy was insufficient. Teneligliptin significantly reduced the HbA1c as compared to placebo from the early stage of dosage administration, and improved glycemic control (See Table 9 and Figures 5, 6 and 7).

Table 9. Glycemic Parameters in 12 Week Placebo-Controlled Study of Teneligliptin in Patients with Type 2 Diabetes (Confirmatory study)

Glycemic Parameters	Teneligliptin 20 mg (N=99)	Placebo (N=104)
A1C (%)	**N=97**	**N=96**
Baseline	7.53 (0.78)	7.58 (0.85)
Change from baseline*	-0.62 (0.05)	0.17 (0.05)
Difference from placebo**	-0.79 (-0.94,-0.64)***	-
Patients (%) achieving A1C < 7%	40.9	5.2
FPG (mg/dL)	**N=99**	**N=104**
Baseline	155.0 (30.3)	155.2 (31.6)
Change from baseline*	-19.2 (1.8)	-0.2 (1.8)
Difference from placebo**	-19.0 (-24.0,-13.9)***	
2-hour PPG (mg/dL)	**N=97**	**N=96**
Baseline	241.3 (55.3)	238.0 (59.1)
Change from baseline*	-47.9 (3.5)	-3.2 (3.6)
Difference from placebo**	-44.7 (-54.6,-34.8)***	

* Values are means (s.d.), except least-squares means (s.e.), ** Values are means (s.d.), except least-squares means (95% confidence intervals), *** $p < 0.0001$



* $p<0.001$

Figure 5. Effects of teneligliptin on change in HbA1c (A) and fasting plasma glucose (B)

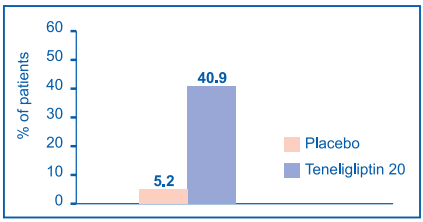


Figure 6. % of patients achieving HbA1c of 7%

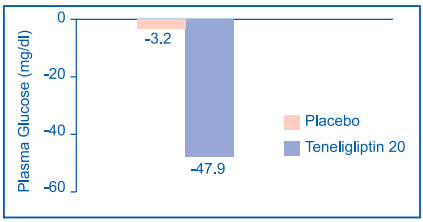


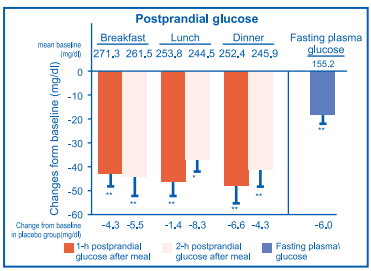
Figure 7. Changes in 2 h PPG from base line to 12 weeks

Long-term administration study

20 mg or 40 mg (when increasing dosage) of teneligliptin was administered once daily for 52 weeks to the patients (151 and 212 cases) having type 2 diabetes mellitus where glycemic control by diet and exercise therapy was insufficient. Teneligliptin significantly reduced the HbA1c level from the early stage of dosage administration, and the change amount (mean value ± standard deviation) of HbA1c level from the dosage start in 52 week was −0.63 ± 0.67% and -0.63 + 0.64%, respectively, and thus, the glycemic control was stabilized over 52 weeks.

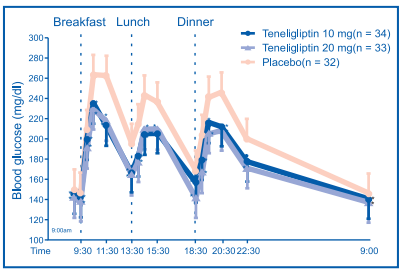
Additional Monotherapy Studies

Ninety-nine patients were administered teneligliptin 10 or 20 mg or placebo before breakfast for 4 weeks in a randomized, double-blind, placebo-controlled, parallel-group study to assess blood glucose control over 24-h and the safety of teneligliptin in type 2 diabetes mellitus inadequately controlled with diet and exercise. Both teneligliptin-treated groups showed significantly smaller 2-h postprandial glucose (2-h PPG), 24-h mean glucose and fasting plasma glucose values than the placebo group. The differences between the teneligliptin 20 mg and placebo groups in changes in 2-h PPG after each meal were 38.1 ± 7.8, -28.6 ± 9.2 and - 36.1 ± 7.5mg/dl at breakfast, lunch and dinner, respectively [least squares (LS) means ± standard error (s.e.), all, $p < 0.001$]. (See Figures 8 & 9)



* p<0.01, ** p<0.001 versus placebo group

Figure 8. Effects of teneligliptin on 1- or 2-h PPG after each meal & FPG at week 4



* p<0.05, versus placebo group

Figure 9. 24 h mean glucose profiles

In another study, drug naive subjects with type 2 diabetes (T2DM) were assigned to 20 mg/day teneligliptin monotherapy (n = 31). After 12 weeks of treatment significant reductions of HbA1c (from 10.34 ± 2.06 to 8.38 ± 2.23%) and fasting blood glucose (FGB, from 211.3 ± 68.4 to 167.3 ± 70.2 mg/dL) levels were observed without any clinically significant adverse events.

Combination Therapy

Teneligliptin added to metformin

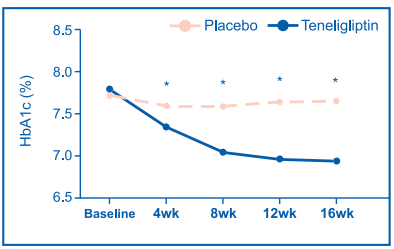
A total of 204 patients with type 2 diabetes participated in a 16-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of teneligliptin in combination with metformin. Patients with type 2 diabetes were eligible to participate if they had inadequate glycemic

control {(HbA1c) levels 7.0–10.0% on stable-dose of metformin monotherapy (≥1000mg/day) for at least 8weeks}. After the 2-week run-in period, eligible patients were assigned 2:1 to a 20mg teneligliptin once daily (N=136) or a placebo once daily (N=68) group, respectively. The metformin dose was kept constant throughout the study period. In combination with metformin, teneligliptin provided significant improvements in A1C, and 2-hour PPG compared to placebo with metformin (See Table 10 and Figures 10 and 11).

Table 10. Glycemic Parameters at Final Visit (16-Week Study) for Teneligliptin (20 mg) in Add-on Combination Therapy with Metformin

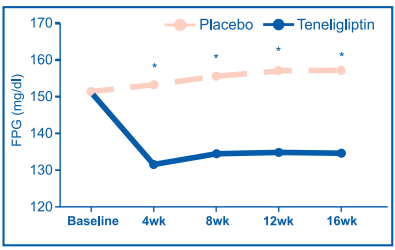
Glycemic Parameters	Teneligliptin + Metformin	Placebo + Metformin
A1C (%)	**(N=136)**	**(N=68)**
Baseline (Mean ± SD)	7.79(0.80)	7.72(0.65)
Change from baseline (Mean ± SD)	-0.87 (0.65)*	-0.06 (0.55)
Difference from placebo (LSM) (95% CI)	-0.90 (-0.95, -0.61)*	-
Patients (%) achieving A1C < 7%	64.7	13.24
2-hour PPG (mg/dL)		
Baseline	151.17 (35.5)	151.17 (25.8)
Change from baseline (Mean ± SD)	-16.8 (24.7)*	5.8(26)
Difference from placebo (LSM) (95% CI)	-20.0 (-29.0,-15.9)*	-

* p < 0.0001



* p<0.001 vs. placebo

Figure 10. Change in HbA1C in patients treated with teneligliptin plus metformin or placebo plus metformin



* p<0.001 vs. placebo

Figure 11. Change in FPG in patient treated with teneligliptin plus metformin or plus placebo or placebo plus metformin

Teneligliptin added to glimepiride in a randomized, double-blind, placebo-controlled study with an open-label, long-term extension study

A randomized, double-blind, placebo-controlled, parallel group, phase III study was conducted to confirm the efficacy and safety of adding teneligliptin to glimepiride in T2DM patients. This study consisted of a 4-week, single-blind, run-in period in which patients received placebo, followed by a 12-week randomized double-blind period in which patients were treated with teneligliptin 20mg (N=96) or placebo (N=98), and a 40-week open-label period in which all patients were treated with teneligliptin 20 or 40 mg. The study drug was taken orally before breakfast every morning throughout the study. The glimepiride dose was set at 1–4 mg/day, and was continued unchanged throughout the study period. Patients who completed the double-blind period entered the open-label period; in which placebo was switched to teneligliptin 20mg (P/T group) or teneligliptin was continued (T/T group). The changes in HbA1c (See Figure 12), FPG, 2-h PPG from baseline to week 12 (double-blind period) and from baseline to week 52 (open-label period) in placebo, T/T and P/T groups is shown in Table 11.

Table 11. Glycemic parameters at completion of double blind period (week 12) and open label period (week 52) for teneligliptin in add-on combination therapy with glimepiride

	Week 0	Week 12	Week 52	Change from Week 0 to Week 12	Teneligliptin *vs.* placebo at Week 12	Change from baseline to Week 52
	Mean (SD)	Mean(SD)	Mean (SD)	LS mean (SE)	LS mean (SE) 95% CI	Mean (SD) 95% CI
HbA1c (%)						
Placebo	8.4 (0.8)	8.7 (0.9)		0.3 (0.1)		
Teneligliptin (T/T)	8.4 (0.8)	7.7 (0.7)	7.8 (1.0)	-0.7 (0.1)	-1.0 (0.1) (-1.2, -0.9)*	-0.6 (0.9) (-0.7, -0.4)*
P/T		8.7 (0.9)	7.8 ± 1.1			-0.9 (0.8) (-1.1, -0.8)*
FPG (mg/dL)						
Placebo	163.4 (31.3)	173.8 (32.8)		9.7 (2.2)		
Teneligliptin (T/T)	165.1 (24.5)	147.5 (23.1)	157.4 (35.2)	-17.4 (2.2)	-27.1 (3.2) (-33.3,-20.9)*	-7.7 (35.6) (-15.0, 0.5)**
P/T		173.8 (32.8)	158.1±36.7			-14.4 (26.3) (-19.8, -9.0)*
2-hour PPG (mg/dL)						
Placebo	256.1 50.5)	262.8 (56.9)		6.0 (4.4)		
Teneligliptin (T/T)	258.6 42.7)	216.6 (48.7)	227.3 (52.1)	-43.1 (4.4)	-49.1 (6.2) (-61.4, -36.7)*	-32.8 (47.3) (-43.1, -22.5)*
P/T		262.8 (56.9)	226.6 (59.4)			-35.6 (45.4) (-45.2, -25.9)*

* p value < 0.001, ** p value < 0.05

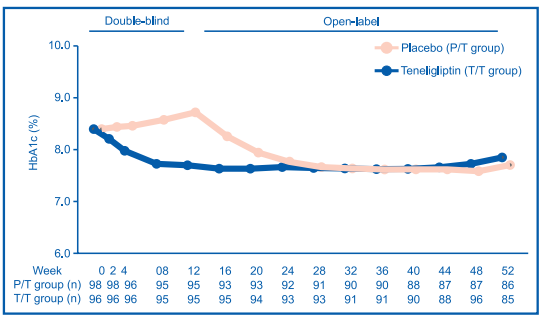


Figure 12. Time course of HbA1c for teneligliptin in add-on combination therapy with glimepiride

Teneligliptin added to pioglitazone in a randomized, double-blind, placebo-controlled study with an open-label, long-term extension study

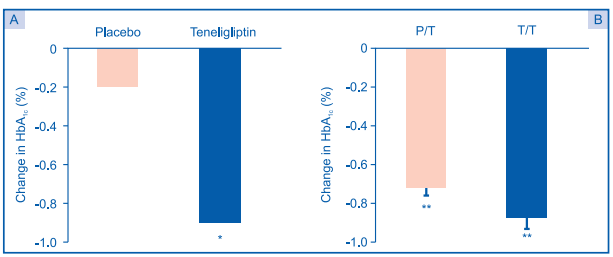
A randomized, double-blind, placebo-controlled, parallel group, phase III study was conducted to confirm the efficacy and safety of adding teneligliptin to pioglitazone in T2DM patients. This study consisted of a 4-week, single-blind, run-in period in which patients received placebo, followed by a 12-week randomized double-blind period in which patients were treated with teneligliptin 20mg (N=96) or placebo (N=98), and a 40-week open-label period in which all patients were treated with teneligliptin 20 or 40 mg.

The study drug was taken orally before breakfast every morning throughout the study. The pioglitazone dose was set at 15 or 30 mg/day, and was continued unchanged throughout the study period. Patients who completed the double-blind period entered the open-label period; in which placebo was switched to teneligliptin 20mg (P/T group) or teneligliptin was continued (T/T group). The changes in HbA1c, FPG, 2-h PPG from baseline to week 12 (double-blind period) and from baseline to week 52 (open-label period) in placebo, T/T and P/T groups is shown in Table 12. (See Figures 13 and 14)

Table 12. Glycemic parameters at completion of double blind period (week 12) and open label period (week 52) for teneligliptin in add-on combination therapy with pioglitazone

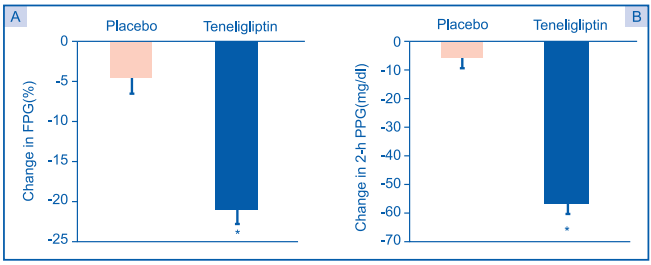
	Week 0	Week 12	Week 52	Change from Week 0 to Week 12	Teneligliptin *vs.* placebo at Week 12	Change from baseline to Week 52
	Mean (SD)	Mean (SD)	Mean (SD)	LS mean (SE)	LS mean (SE) 95% CI	Mean (SD) 95% CI
HbA1c (%)						
Placebo	7.9 (0.8)	7.8 (0.8)		-0.2 (0.0)		
Teneligliptin (T/T)	8.1 (0.9)	7.1 (0.7)	7.2 (0.7)	-0.9 (0.0)	-0.7 (0.1) (-0.9, -0.6)*	-0.9 (0.7) (-1.0, -0.7)*
P/T		7.8 (0.8)	7.0 (0.5)			-0.7 (0.7) (-0.9, -0.6)*
FPG (mg/dL)						
Placebo	145.7 (26.5)	140.8 (27.6)		-4.5 (2.0)		
Teneligliptin (T/T)	150.7 (28.1)	128.3 (20.6)	138.6 (27.9)	-21.0 (1.9)	-16.4 (2.8) (-21.9,-11.0)*	-12.1 (26.2) (-17.2, 6.9)**
P/T		140.8 (27.6)	131.8 (21.7)			-9.1 (20.6) (-13.2, -4.9)*
2-hour PPG (mg/dL)						
Placebo	221.5 (55.3)	218.8 (56.0)		-5.6 (3.6)		
Teneligliptin (T/T)	230.9 (57.9)	172.5 (40.0)	190.2 (48.6)	-56.9 (3.6)	-51.3 (5.2) (-61.4, -41.1)*	-37.5 (47.1) (-47.5, -27.5)*
P/T		218.8 (56.0)	177.4 (43.1)			-41.5 (46.6) (-51.2, -31.8)*

* p value < 0.001



* p<0.01 versus placebo group, ** p<0.001 versus baseline

Figure 13. Change in HbA1C at completion of double blind period (week 12) (A) and open label period (week 52) (B) for teneligliptin in add-on combination therapy with pioglitazone



* p<0.001 vs placebo

Figure 14. Effects of teneligliptin and placebo on change from baseline in FPG (A) and 2 h PPG (B) at the end of double blind period (week 12)

Teneligliptin added to sulfonylureas, glinides, biguanides and α-glucosidase inhibitors in a long term (52 weeks) safety and efficacy study

20 mg or 40 mg (when increasing dosage) of teneligliptin was administered once daily for 52 weeks to the patients having type 2 diabetes mellitus where glycemic control by sulfonylureas (N=89), glinides (N=80), biguanides (N=95), and α-glucosidase inhibitor (N=75), in addition to diet and exercise therapy, was insufficient. Teneligliptin significantly reduced the HbA1c level from the early stage of dosage administration, and the change amount (mean value ± standard deviation) of HbA1c level from the dosage start in 52-week was -0.81 ± 0.76%, −0.76±0.70%, −0.78±0.75%, and −0.89±0.64%, respectively, and thus, the glycemic control was stabilized over 52 weeks.

Teneligliptin added to insulin: a prospective, non-blinded, pilot study

Twenty-six patients with type 2 diabetes were admitted for glycemic control. After admission, patients continued to be treated with optimal dietary therapy plus insulin therapy, with or without other antidiabetic drugs, until they achieved stable glycemic control. Continuous glucose monitoring (CGM) measurements were made for 7 consecutive days. On Days 1–3, patients received insulin with or without other antidiabetic drugs, and on Days 4–7, teneligliptin 20 mg once daily at breakfast was added to ongoing therapy. Doses of insulin were fixed during the study. Add-on treatment with teneligliptin led to significant improvements in 24-h mean glucose levels, the proportion of time in normoglycemia, mean amplitude of glycemic excursions, and total area under the curve within 2 h after each meal (See Table 13 and Fig 15 & 16).

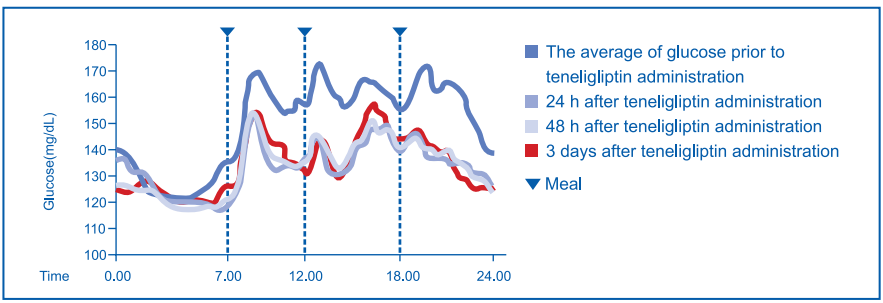


Figure 15. The 24-h glucose profiles before and after administration of teneligliptin

Table 13. Glucose variability parameters before and after treatment with teneligliptin (n = 26)

	Insulin therapy	
	Before Teneligliptin treatment	After Teneligliptin treatment
Mean glucose level (mg/dL)	148.8 ± 25.7	131.3 ± 17.0[a]
0:00-7:00 h	126.0 ± 7.5	119.0 ± 4.2[a]
7:00-24:00 h	159.1 ± 9.8	138.0 ± 9.1[a]
Postprandial glucose level (mg/dL) within 2 h after meal		
Breakfast	152.8 ± 9.0	140.0 ± 10.9[a]
Supper	164.8 ± 2.7	135.4 ± 4.9[a]
Dinner	165.8 ± 5.3	142.6 ± 5.1[a]
SD over 24 h (mg/dL)	32.0 ± 16.2	26.9 ± 10.9[a]
Proportion (%) of time in		
Hypoglycemia (< 70 mg/dL)	1.0 ± 2.4	1.6 ± 2.6
Appropriate glucose level (70-140 mg/dL)	38.3 ± 24.5	59.0 ± 20.3[a]
Hyperglycemia (> 140 mg/dL)	59.8 ± 24.7	37.6 ± 22.4[a]
MAGE (mg/dL)	90.1 ± 46.7	85.5 ± 34.3[b]
Total AUC (mg/dL/h) for glycemic variability within 2 h of each meal		
Breakfast	31.9 ± 5.8	29.0 ± 5.3[a]
Supper	33.1 ± 6.4	27.7 ± 5.7[a]
Dinner	33.4 ± 8.1	28.4 ± 5.1[a]

Data are mean ± SD values; [a]p value < 0.001, [b]p value < 0.05 versus before teneligliptin administration.
AUC - area under the curve; MAGE - mean amplitude of glycemic excursions

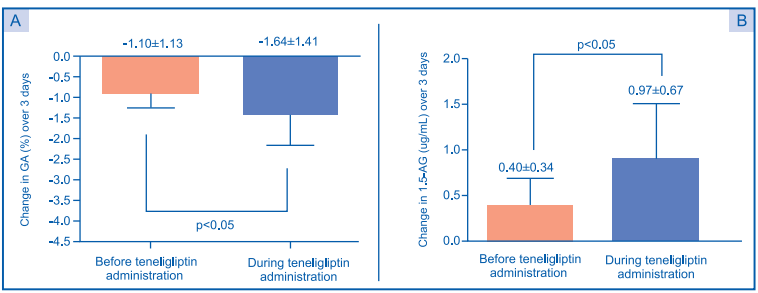


Figure 16. Changes in [A] glycated albumin (GA), [B] 1,5-anhydro-d-glucitol (1,5-AG) with administration of teneligliptin

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