Assessment of efficacy and safety of teneligliptin in patients with type 2 diabetes mellitus having hypertension/dyslipidemia

Synopsis of the PhD thesis submitted to

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by

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a. Title of the thesis and abstract

Title: Assessment of efficacy and safety of teneligliptin in patients with type 2 diabetes mellitus having hypertension/dyslipidemia

Abstract:

Background: Diabetes is a progressive disease which include both microvascular and macrovascular complications. Therefore, rigorous efforts have been made to lower blood glucose levels and prevent diabetic complications.Teneligliptin, a novel highly selective dipeptidyl peptidase-4 inhibitor.

Objective: To evaluate efficacy and safety of teneligliptin in type 2 diabetes mellitus patients having dyslipidemia and hypertension.

Methods: Clinical study protocol was approved by the Institutional Ethics Committee (IEC Reg. No: **ECR/274/Inst/GJ/2013/RR-19.,**Dr.Jivraj Mehta Smarak Hospital, Ahmedabad, Gujarat). Study was conducted in four phases, each phase include 120 subjects according to randomization which is mentionedas under: **Study phase I: Diabetic patients with add on teneligliptin**(Treatment A: Standard anti-diabetic therapy (Metformin + Glimeperide) and Treatment B: Standard anti-diabetic therapy (Metformin + Glimeperide) and add on teneligliptin (20mg))., **Study Phase-II: Diabetic patients having dyslipidemia** (Treatment A: Statin (Atorvastatin)treatment and anti-diabetic therapy (Metformin + Glimeperide)&Treatment B: Statin (Atorvastatin) and anti-diabetic therapy (Metformin + Glimeperide) with add on teneligliptin (20mg))., **Study Phase-III: Diabetic patients having hypertension**(Treatment A: Antihypertensive (Telmisartan) and anti-diabetic therapy (Metformin + Glimeperide) &Treatment B: Antihypertensive (Telmisartan) and anti-diabetic therapy (Metformin + Glimeperide) with add on teneligliptin (20mg))., and **Study Phase-IV: Diabetic patients having dyslipidemia and hypertension**(Treatment A: Standard antihypertensive (Telmisartan), and statin (Atorvastatin) treatment with standard anti-diabetic therapy (Metformin + Glimeperide)& Treatment B: Standard antihypertensive (Telmisartan), statin (Atorvastatin)and anti-diabetic therapy (Metformin + Glimeperide) with add on teneligliptin (20mg) for 24 weeks of treatment duration of each study phase. Predesigned case report form (CRF) was used to collect information from the prescribing physicians regarding the efficacy and safety of teneligliptin with respective study phases. Efficacy variables viz. change in serum glycaemic, lipid, blood pressure and cytokine (IL-6, TNF-α andadiponectin) levels from baseline to end of 24 weeks were measured. Treatment-emergent adverse events (TEAEs) were also assessed for respective phase of study.

Statistical Analysis Plan (SAP): Categorical data were presented as absolute number of patients while quantitative data was presented as mean ± standard deviation (SD). Within group comparison was performed using paired t-test based on the distribution of data. Unpaired t-test was used to analyse the quantitative data for between group comparisons.

Correlations were studied by Spearman's rank correlation coefficient analysis. P value of less than 0.05 was considered as statistical significant difference. Data were calculated using Graph Pad prism version 5.0.

Results: Study phase I (**Diabetic patients with add on teneligliptin**): The addition of teneligliptin to glimepiride + metformin resulted in significant reduction in glycemic parameters (HbA1c, FBG, and PPBG) compared to glimepiride + metformin therapy.Teneligliptin, add on therapy showed marked reduction in serum IL-6 and TNF alpha levels and significantly improved adiponectin levels in diabetic patients.**Study Phase-II(Diabetic patients having Dyslipidemia):** Teneligliptin, as add on therapy to conventional therapy significantly reduced serum lipid profile (TC, TG, and LDL) as well as glycaemic parameters (HbA1c, FBG, and PPBG) along with significant rise in serum adiponectin levels as compared to conventional therapy.**Study Phase-III (Diabetic patients having Hypertension):** Teneligliptin, as add on treatment to conventional therapy significantly reduced serum glycaemic parameters (HbA1c, FBG, and PPBG) along with marked rise in serum adiponectin levels as compared to conventional therapy.Blood pressure was also improved in patient with concomitant hypertension.**Study Phase-IV (Diabetic patients having Dyslipidemia and Hypertension):**It has been observed in our study that teneligliptin, as add on therapy is found well tolerated and effective in T2DM patients having dyslipidemia and hypertension. Tenligliptin add on treatment with atorvastatin and telmisartan was found effective along-with conventional-therapy in reducing hyperglycaemia as well as improving lipid profile as well as blood pressure control in diabetic patients having dyslipidemia and hypertension.

Conclusion: Add- on therapy with teneligliptin was found superior over conventional therapy that is evident from the significant reduction of glycaemic parameters.In addition, significant rise in serum adiponectin levels was observed inteneligliptintreated patients as compared to conventional therapy.

b. Brief description on the state of the art of the research topic:

Diabetes mellitus (DM), a chronic metabolic non-communicable disease (NCD), has attained epidemic proportions worldwide (1-2).The countries with the largest number of diabetic people are, and will be in the year 2025, India, China and United States(3). The global prevalence of diabetes is estimated to increase, from 4% in 1995 to 5.4% by the year 2025(4).

Although a number of antihyperglycemic agents are available for glucose-lowering therapy, it is still difficult to maintain good glycemic control with the existing drugs over a long-term period because of the progressive pathophysiology of T2DM (5-8). Patients with inadequate glycemic control often require additional combination therapy or treatment with newer anti-diabetic agents or insulin to achieve the desired glycemic target levels(9-12).

DPP-4 inhibitor is expected to be used safely for the treatmentof type 2 diabetes because it has no risk of hypoglycemia and/or weight gain (13-15). However, not much work has been done to evaluate the cardiac efficacy and safety of DPP-4 inhibitors. Hence, we propose to study the assessment of efficacy and safety of teneligliptin in type 2 diabetes mellitus patients having dyslipidemia and hypertension.

c. Definition of the Problem:

Patients are frequently prescribed antidiabetic drugs which can cause hypoglycemia, and/or weight gain (16-17). DPP-4 inhibitor is expected to be used safely for the treatment of type 2 diabetes because it has no risk of hypoglycemia and/or weight gain which are reported in pre-existing diabetes therapies and no inconvenience related to dose adjustment depending on patient's condition (18-20).

A tight glucose controlreduces microvascular and macrovascular complicationsthat mightlead to reduction of the associated risk factors, including those related to excessive weight, high blood pressure and dyslipidemia are also necessary to meaningfully decrease the cardiovascular risk (21-22).

As there is no long term studies conducted on add-on therapy of teneligliptin, our study was designed to evaluate efficacy, safety, tolerability and affordability treatment for diabetic patients having dyslipidemia and hypertension in India.

d. Objective and Scope of work:

Objective:

Primary objective: To evaluate efficacy of teneligliptin in patients with type 2 diabetes mellitus patients having dyslipidemia and hypertension.

Secondary objective: To evaluate safety and tolerability ofteneligliptin in patients with type 2 diabetes mellitus patients having dyslipidemia and hypertension.

Scope:

Possible therapeutic benefit of Teneligliptin a novel DPP-4 inhibitor in diabetic patients having dyslipidemia and hypertension was ascertained scientifically and will be published in reputed international medicinal journals, so doctors, physicians, research scholar and patients can aware the benefit and risk of teneligliptin and also know about add on treatment with respective co-morbid condition.Our findings towards efficacy, tolerability and safety of teneligliptinin diabetic patients having dyslipidemia and hypertension would translate to global marketing opportunities for teneligliptin.

e. Original contribution by the thesis:

The current clinical study provided scientific data including efficacy, safety, tolerability, and mechanism of action regarding potential use of teneligliptin 20 mg/day in diabetic patients having dyslipidemia and hypertension in India. Therapeutic dose regimen and newer pharmacological management will be established for diabetic patients having dyslipidemia and hypertension.

f. Methodology of Research, Results / Comparisons:

1. Methods:

a. Ethics Approval: This study was conducted at Jivraj Mehta Hospital and Bakeri Medical Research Centre, Ahmedabad. The study protocol, informed consent form (ICF) and relevant essential documents were approved by Institutional Ethics Committee (IEC) (IEC registration No: ECR/274/Inst/GJ/2013/RR-19); Safety, Health and welfare Ethics committee, registered under Drug Controller General of India (DCGI).

b. Study Plan:

Study plan was mentioned below:

Study Phase-I: Diabetic patients with add on teneligliptin (n=120):

A total 120 T2DM patients (male/female) whose glycated hemoglobin (HbA1c) >7% were randomized in 1:1 ratio to receive either metformin (500 mg/day) and glimepiride(2 mg/ day) (Treatment A) and metformin(500 mg/day) and glimepiride(2 mg/day) plus add-on teneligliptin(20 mg/day)(Treatment B) for 24 weeks (23-24). A pre-designed case report form was used to collect information from the prescribing physicians regarding the efficacy and safety of teneligliptin. The efficacy endpoint was evaluated the change in HbA1c, FBG, and PPBG from baseline to 24 weeks. Safety was measured by recording AEs including symptomatic assessment by Naranjo causality scale for AE (25). The incidence of AE in terms of number per patient was calculated based on the number of events, the number of patients and the total observation period.

Study Phase-II: Diabetic patients having Dyslipidemia (n=120):

Diabetic patients having dyslipidemia (male/female) were randomized to receive treatments in two groups. Eligible patients were randomized in 1:1 ratio to receive either metformin (500 mg/day) + glimepiride (2 mg/day) and atorvastatin (20 mg/day) (Treatment A) or metformin (500 mg/day) + glimepiride (2 mg/day), atorvastatin (20 mg/day) and add on teneligliptin (20 mg/day) (Treatment B) for 24 weeks. Patient's demographics data, physical and clinical examination, AEs, and laboratory assessments were documented in predesigned case report form(CRF).

Efficacy variables included change in Lipid profile serum Total cholesterol (TC), Triglyceride (TG), Low density lipoprotein (LDL), High density lipoprotein (HDL) and Glycemic parametersserum glycatedhaemoglobin (HbA1c), fasting blood glucose (FBG) and post prandial blood glucose (PPBG) levels and Inflammatory cytokine levels IL6, TNF-α, and adiponectin levels were measured at baseline and at the end of 24 weeks in both the treatment groups.

Study Phase-III: Diabetic patients having Hypertension (n=120):
Diabetic patients (male/female) having hypertension were randomized in 1:1 ratio to receive either metformin (500mg/day) plus glimepiride (2 mg/day) and telmisartan (20 mg/day) (treatment A) or metformin (500mg/day) plus glimepiride (2 mg/day), telmisartan (20 mg/day), and add on teneligliptin (20 mg/day) (Treatment B) for 24 weeks. Efficacy variables included change in blood pressure, serum glycaemic, and cytokines (IL-6, TNF- α and adiponectin) levels from baseline to week 24. Treatment-emergent adverse events (TEAEs) were also assessed.

Study Phase-IV: Diabetic patients having Dyslipidemia and Hypertension (n=120):
Diabetic patients having dyslipidemia and hypertension (male/female) were randomized to receive treatments in two groups. Eligible patients were randomized in 1:1 ratio to receive either metformin (500 mg/day) + glimepiride (2 mg/day) temisartan and atorvastatin (20 mg/day) (Treatment A) or metformin (500 mg/day) + glimepiride (2 mg/day), temisartan , atorvastatin (20 mg/day) and add on teneligliptin (20 mg/day) (Treatment B) for 24 weeks. Patient's demographics data, physical and clinical examination, AEs, and laboratory assessments were documented in predesigned case report form (CRF). Efficacy variables included change in Lipid profile serum Total cholesterol (TC), Triglyceride (TG), Low density lipoprotein (LDL), High density lipoprotein (HDL), and blood pressureand Glycemic parameters serum glycatedhaemoglobin (HbA1c), fasting blood glucose (FBG) and post prandial blood glucose (PPBG) levels and Inflammatory cytokine levels IL6, TNF-α, and adiponectin levels were measured at baseline and at the end of 24 weeks in both the treatment groups.Treatment-emergent adverse events (TEAEs) were also assessed.

c. **Statistical Analysis Plan (SAP):** Categorical data were presented as absolute number of patients while quantitative data was presented as mean ± standard deviation (SD). Within group comparison was performed using paired t-test based on the distribution of data. Unpaired t-test was used to analyse the quantitative data for between group comparisons. Correlations were investigated by Spearman's rank correlation coefficient analysis. P value of less than 0.05 was considered as statistical significant difference. Data were calculated using Graph Pad prism version 5.0.

Results:

Study Phase-I: Diabetic patients with add on teneligliptin:

Table-1: Demographic and clinical characteristic

Patient characteristic	Treatment A (N=60)	Treatment B (N=60)
Demographic		
Gender(Male/Female)	30/30	34/26
Age (year)	50.73± 12.08	49.81±14.29
Height (cm)	155.93 ± 8.12	157.6 ± 9.55
Body Weight (kg)	62.43 ± 9.11	62.55 ±8.18
Body mass index (BMI)	25.79 ± 4.01	25.35 ± 4.00
Disease duration (year)	3.98± 2.00	3.46 ± 1.65

Treatment A: Conventional treatment and Treatment B: Conventional treatment plus add on teneligliptin 20 mg. N=number of patient, SD= standard deviation. Values are expressed as Mean ± standard deviation.

Table-2: Change in blood glucose levels (fasting and post prandial) and HbA1C from baseline to 24 weeks after study drug treatments

Parameters	Treatment A (N=60)	Treatment B (N=60)
Haemoglobin A_1C (HbA_1c)		
Baseline (HbA_1c)	9.88 ± 1.69	10.75 ± 2.07
End of 24 weeks	9.12 ± 1.72*	9.55 ± 1.94*
Change in HbA1C	0.76 ± 0.32	1.20 ± 0.50$^{@}$
Fasting blood glucose (FBG)		
Baseline (FBG)	170.66 ± 40.35	177.31 ± 48.96
End of 24 weeks (FBG)	143.25 ± 36.11*	136.23 ± 31.67*
Change in Fasting	27.41 ± 14.56	41.08 ± 35.02 $^{\#}$
Post prandial blood glucose (PPBG)		
Baseline (PPBG)	246.43 ± 58.30	258.41 ± 53.74
End of 24 weeks (PPBG)	211.62 ± 51.96*	204.3 ± 49.91*
Change in post prandial	34.80 ± 25.18	54.11 ± 35.77 $^{\$}$

Treatment A: Conventional treatment and Treatment B:Conventional treatment plus add on teneligliptin 20 mg. N=number of patient, SD= standard deviation. Values are expressed as Mean± standard deviation. * $p<0.05$ from baseline by paired t test (within group comparison). @ indicate change in HbA1C from the baseline to 24 weeks; # indicate change in Fasting blood glucose (FBG) from the baseline to 24 weeks; $ indicate change in Post prandial blood glucose (PPBG) from the baseline to 24 weeks. Between groups comparison was done using un-paired t test.

Table-3: Summary of adverse events:

Adverse event (AE)	Treatment A N=60 (%)	Treatment B N=60 (%)
Hypoglycemia	2 (3.33%)	2 (1.00%)
Constipation	5 (8.33%)	4 (6.66%)
Abdominal Pain	5 (1.00%)	3 (5.00%)
Acidity	2 (3.33%)	6 (1.00%)
Tingling	1 (1.00%)	3 (5.00%)
Tiredness	2 (3.33%)	2 (3.33%)
Weakness	2 (3.33%)	2 (3.33%)
Pain	2 (3.33%)	2 (3.33%)
Headache	1 (1.00%)	3 (3.33%)
dry skin	3 (5.00%)	1 (1.00%)
Itching	2 (3.33%)	2 (3.33%)
Total	**27 (45%)**	**30 (50%)**

Treatment A: Conventional treatment and Treatment B: Conventional treatment plus add on teneligliptin 20 mg. N= Number of patient

Study Phase-II: Diabetic patients having Dyslipidemia:

Table 4: Demographic and clinical characteristic

Characteristic	Treatment A (N=60)	Treatment B (N=60)
Demographic		
Gender(Male/Female)	31/29	34/26
Age (year)	48.56 ± 8.66	50.41 ± 7.27
Height (cm)	159.9 ±10.47	164.21 ± 8.80
Body Weight (kg)	69.06 ± 17.79	76.90 ± 13.40
Body mass index (BMI)	25.85 ± 3.84	28.67 ± 4.76
Disease duration (year)	4.56 ± 1.61	4.86 ± 1.50
Waist (cm)	92.93 ± 8.86	95.72 ± 10.07
Hip (cm)	98.63 ±10.33	102.33 ± 11.33
Pulse /min	87.16 ±13.96	85.96 ± 13.01
Systolic blood pressure (mmHg)	132.9 ±18.70	132.97 ± 18.85
Diastolic blood pressure (mmHg)	80.91 ±8.66	80.28 ± 10.19

Treatment A: Conventional treatment and Treatment B: Add on teneligliptin with conventional treatment. Values are expressed as Mean±SD. N=number of patient, SD= standard deviation

Table 5: Mean change in blood lipid and glycemic levels from baseline to 24 weeks after study drug treatments

Parameters	Treatment A (N=60)	Treatment B (N=60)
Total cholesterol (TC)		
Baseline (TC)	218.08± 20.15	219.00 ±14.18
End of 24 weeks	176.78 ±13.22*	166.90 ±19.56*
Change in TC	41.22±18.57 (18.90%)	52.10 ±20.92$^{\#}$ (23.78%)
Triglyceride (TG)		
Baseline (TG)	190.88 ±18.62	197.36 ±18.00
End of 24 weeks (TG)	160.13 ±18.60*	157.88 ±17.30*
Change in TG	30.75±11.56 (16.10%)	39.48 ±15.25$^{\#}$ (20.00%)
High density lipoprotein (HDL)		
Baseline (HDL)	36.44 ±4.38	37.32 ± 5.47
End of 24 weeks (HDL)	39.08 ±4.61*	40.56±5.53*
Change in HDL	2.64 ± 0.98 (7.24 %)	3.24 ±1.08 (8.68%)
Low density lipoprotein (LDL)		
Baseline (LDL)	158.54 ±13.15	155.90 ±17.39
End of 24 weeks (LDL)	113.76 ±17.03*	103.09 ±17.76*
Change in LDL	44.78±11.61 (28.24%)	52.80 ±15.77$^{\#}$ (34.06%)
TC/HDL ratio (atherogenic Index)		
Baseline	6.07±0.94	6.06±1.05
End of 24 weeks	4.59±0.69*	4.17±0.66*
Change in ration TC/HDL	1.48±0.53 (24.38%)	1.82±0.76 (30.03%)
Glycatedheamglobin (HbA1c)		
Baseline	9.63 ±1.24	9.45 ±1.27
End of 24 weeks	8.67 ±1.29*	8.24 ±1.21*
Change in HbA1c	0.96 ±0.46(9.96%)	1.20 ±0.45$^{\$}$(12.69%)
Fasting blood glucose (FBG)		
Baseline	153.54 ±20.95	157.53±19.82
End of 24 weeks	129.98±16.65*	124.91 ±18.54*
Change in FBG	23.56±8.40(15.34%)	32.62±11.45$^{\$}$(20.70%)
Post prandial blood glucose (PPBG)		
Baseline	248.46 ±27.35	252.82± 27.58
End of 24 weeks	219.56 ±27.67*	216.19± 25.92*
Change in PPBG	28.89 ± 9.17(11.62%)	36.62± 9.92$^{\$}$(14.48%)
Inflammatory cytokines		
IL 6 (pg/ml)		
Baseline	8.027±0.92	7.927±0.93

End of 24 weeks	7.607±0.97*	7.409±0.99*
Change in IL 6	0.420±0.38 (5.23%)	0.518±0.29 (6.43%)
TNF-α(pg/ml)		
Baseline	15.728±1.92	15.348±1.69
End of 24 weeks	15.178±1.85*	14.597±1.65*
Change in TNF-α	0.550±0.42 (3.48%)	0.751±0.42 (4.88%)
Adiponectin(µg/ml)		
Baseline	4.441±0.84	4.673±0.93
End of 24 weeks	5.069±1.32*	9.449±1.44*
Change in adiponectin	0.629±0.87 (14.16%)	4.776±1.68@ (102%)

Values are expressed as Mean±SD. N=number of patient, SD= standard deviation Treatment A: Conventional treatment and Treatment B: Add on teneligliptin with conventional treatment. * $p<0.05$ from baseline to end of 24 weeks by using paired t test (within group comparison).$ $p<0.05$indicate change in Glycaemic parameter (HbA1c, FBG, and PPBG) from the baseline to 24 weeks; # $p<0.05$ indicate change in lipid parameters (TC, TG, and LDL) from the baseline to 24 weeks;@ $p<0.05$ indicate change in adiponectin level from the baseline to 24 weeks;between groups comparison was done using un-paired t test.

Table 6: Summary of adverse events

Adverse event (AE)	**Treatment A N=60 (%)**	**Treatment B N=60 (%)**
Hypoglycemia	2 (3.33%)	2 (3.33%)
Constipation	5 (8.33%)	2 (3.33%)
Abdominal Pain	6 (10.00%)	3 (5.00%)
Acidity	4 (6.66%)	3 (5.00%)
Weakness	2 (3.33%)	2 (3.33%)
Headache	2 (3.33%)	1 (1.66%)
Total	**21(35%)**	**13(21.66%)**

Treatment A: Conventional treatment and Treatment B: Add on teneligliptin with conventional treatment

Study Phase-III: Diabetic patients having Hypertension

Table 7: Demographic profile and clinical characteristic

Characteristic	Treatment A (N=60)	Treatment B (N=60)
Demographic		
Gender(Male/Female)	24/36	28/32
Age (year)	48.56 ± 9.45	48.16 ± 7.64
Height (cm)	152.12 ±13.59	156.21 ± 10.69
Body Weight (kg)	68.28 ± 10.76	67.79 ±11.12
Body mass index (BMI)	26.81 ±3.78	26.24 ± 4.33
Disease duration (year)	3.54 ± 1.48	3.71 ± 2.05
Waist (cm)	91.48 ±7.03	91.68 ±7.24
Hip (cm)	96.56±8.83	96.88 ±8.32
Diet history (calories)		
• Breakfast (calories)	1452.56 ± 296.85	1445.08 ± 284.44
• Lunch (calories)	2080.33 ± 406.33	156.21 ± 10.69
• Dinner (calories)	642.81 ± 210.74	646.14 ± 214.74
Vegetarian/ Non-vegitarian	45/15	49/11
Job/ Business	44/16	38/22
Exercise/ Yoga	47/13	47/13

Values are expressed in terms of Mean± SD. N=number of patient, SD= standard deviation. Treatment A: Conventional treatment and Treatment B: Add on teneligliptinwith conventional treatment.

Table 8: Mean change in blood pressure and glycemic levels from baseline to 24 weeks after study drug treatments:

Parameters	Treatment A (N=60)	Treatment B (N=60)
Glycatedheamglobin (HbA1c)		
Baseline	8.31 ± 0.84	8.23 ± 0.83
End of 24 weeks	7.64 ±0.81*	7.47 ± 0.72 *
Change in HbA1c	0.66 ±0.21	0.766 ±0.26 $
Fasting blood glucose (FBG)		
Baseline	148.63± 16.52	149.01±16.27
End of 24 weeks	120.71 ±13.28*	117.40 ±16.24*
Change in FBG	27.91 ±7.13	31.60 ± 7.62$
Post prandial blood glucose (PPBG)		
Baseline	226.22 ±20.62	221.8± 27.58
End of 24 weeks	195.79 ±20.02*	186.92± 19.87*

Change in PPBG	30.42 ±7.87	35.17± 10.06$
SBP (mm/Hg)		
Baseline	145.11 ±11.20	144.13 ±9.63
End of 24 weeks	140.53 ±11.08*	138.86± 9.96*
Change in SBP	4.58 ±1.93	5.26 ±1.99
DBP (mm/Hg)		
Baseline	84.96 ±5.10	83.13 ±5.72
End of 24 weeks	80.73 ±4.64*	78.33 ±5.30*
Change in DBP	4.23 ±1.81	4.8± 1.84
Cytokines levels		
IL 6 (pg/ml)		
Baseline	7.567 ± 1.246	7.441 ± 1.205
End of 24 weeks	7.095 ± 1.167*	6.798 ± 1.087*
Change in IL 6	0.4710± 0.484	0.643 ±0.530
TNF-α (pg/ml)		
Baseline	16.031 ± 1.764	15.836 ± 1.678
End of 24 weeks	15.505 ± 1.781 *	15.149 ± 1.671*
Change in TNF-α	0.526 ±0.402	0.687 ± 0.393
Adiponectin (µg/ml)		
Baseline	4.029 ± 0.639	4.352 ±0.770
End of 24 weeks	4.773 ± 1.041*	8.895 ± 1.522 *
Change in adiponectin	0.704 ± 1.019	4.543 ± 1.598@

Values are expressed as Mean±SD. N=number of patient, SD= standard deviation Treatment A: Conventional treatment and Treatment B: Add on teneligliptin with conventional treatment. * $p<0.05$ from baseline to end of 24 weeks by using paired t test (within group comparison).**$** $p<0.05$indicate change in Glycaemic parameter (HbA1c, FBG, and PPBG) from the baseline to 24 weeks. **@** $p<0.05$ indicate change in adiponectin level from the baseline to 24 weeks;between groups comparison was done using un-paired t test.

Table 9: Summary of adverse events

Adverse event (AE)	Treatment A N=60 (%)	Treatment B N=60 (%)
Hypoglycemia	1 (1.66%)	1 (1.66%)
Constipation	6 (10.0%)	5 (8.33%)
Abdominal Pain	6 (10.00%)	6 (10.0%)
Acidity	5 (8.33%)	5 (8.33%)
Tiredness	3(5.00%)	2 (3.33%)
Weakness	2 (3.33%)	1 (3.33%)
Dry skin	1(1.66%)	1(1.66%)
Headache	2 (3.33%)	1 (1.66%)
Itching/pruritus	1(1.66%)	1(1.66%)
Total	**27 (45%)**	**23 (38.3%)**

Treatment A: Conventional treatment and Treatment B: Add on teneligliptinwith conventional treatment.

Study Phase-IV: Diabetic patients having Dyslipidemia and Hypertension

Table 10: Demographic and clinical characteristic

Characteristic	Treatment A (N=60)	Treatment B (N=60)
Demographic		
Gender(Male/Female)	30/30	29/31
Age (year)	50.73 ± 12.08	51.48 ± 11.96
Height (cm)	155.93 ± 8.12	156.21 ± 8.12
Body Weight (kg)	62.43 ± 9.11	63.79 ± 9.67
Body mass index (BMI)	25.79 ± 4.01	25.85 ± 4.71
Disease duration (year)	4.79 ± 1.65	5.04 ± 1.61
Waist (cm)	91.88 ± 8.32	92.53 ± 6.68
Hip (cm)	96.56±8.83	96.16±8.01
Waist/hip ratio	0.94±0.5	0.96±0.6

Values are expressed in terms of Mean± SD. N=number of patient, SD= standard deviation. Treatment A: Conventional treatment and Treatment B: Add on teneligliptinwith conventional treatment.

Table 11: Mean change in blood lipid and glycemic levels from baseline to 24 weeks after study drug treatments

Parameters	Treatment A (N=60)	Treatment B (N=60)
Glycatedheamglobin (HbA1c)		
Baseline	9.15 ±1.23	9.27 ± 1.16
End of 24 weeks	8.74 ± 1.26*	8.68 ± 1.19*
Change in HbA1c	0.40 ±0.21	0.58 ±0.25$
Fasting blood glucose (FBG)		
Baseline	141.50± 18.31	146.87±17.40
End of 24 weeks	131.09± 17.51	133.83 ±17.32*
Change in FBG	10.40± 4.64	12.99± 5.34$
Post prandial blood glucose (PPBG)		
Baseline	210.23± 34.74	229.53 ± 22.05
End of 24 weeks	192.86±32.54	209.51 ± 23.90*
Change in PPBG	17.37± 6.23	20.02 ± 7.02$
Systolic blood pressure (mm/Hg) (SBP)		
Baseline	145.23±8.39	148.53± 7.44
End of 24 weeks	143.43±8.27	146.67± 7.47
Change in PPBG	1.8±1.95	1.96± 2.14
Diastolic blood pressure (mm/Hg) (DBP)		
Baseline	81.90±5.22	82.56±5.58
End of 24 weeks	80.43 ±5.07	80.08±5.24
Change in PPBG	1.46±1.70	1.76± 2.13
Inflammatory cytokines		
IL 6 (pg/ml)		
Baseline	8.61±1.11	8.49 ± 1.09
End of 24 weeks	8.25 ± 1.21	7.98 ± 1.22*
Change in IL 6	0.36±0.37	0.51 ±0.42
TNF-α (pg/ml)		
Baseline	16.06 ±1.66	15.80±1.51
End of 24 weeks	15.63±1.60*	15.20 ±1.40*
Change in TNF-α	0.44±0.34	0.65 ±0.39
Adiponectin (µg/ml)		
Baseline	3.96 ±0.73	4.02±0.63
End of 24 weeks	4.35 ±0.77*	4.80 ±1.12*
Change in adiponectin	0.38±1.06	0.776±1.12

Values are expressed as Mean±SD. N=number of patient, SD= standard deviation Treatment A: Conventional treatment and Treatment B: Add on teneligliptin with conventional treatment. *

p<0.05 from baseline to end of 24 weeks by using paired t test (within group comparison).**$** p<0.05indicate change in Glycaemic parameter (HbA1c, FBG, and PPBG) from the baseline to 24 weeks;**@** p<0.05 indicate change in adiponectin level from the baseline to 24 weeks;between groups comparison was done using un-paired t test.

Table 12: Summary of adverse events

Adverse event (AE)	**Treatment A N=60 (%)**	**Treatment B N=60 (%)**
Hypoglycemia	2	2
Constipation	5	4
Abdominal Pain	7	4
Acidity	2	1
Tingling	2	2
Tiredness	1	2
Pain	4	3
Dry skin	3	3
Itching	2	2
Giddiness	1	0
Weakness	3	2
Headache	1	1
Total	**33 (56%)**	**26 (45%)**

Treatment A: Conventional treatment and Treatment B: Add on teneligliptin with conventional treatment

g. Achievements with respect to objectives

Add-on therapy with teneligliptinis found superior over conventional therapy in reducing glycemic levels (HbA1c, FBG, and PPBG) in patients with T2DM. Also, we observed significant reduction of glycemic parameters with add on teneligliptin therapyirrespective of co- morbidities like dsylipidemia or hypertension. We also observed significant rise in serum adiponectin levels with teneligliptin as compared to conventional therapy in study I, II, III and IV.

h. Conclusion:

Study I:Diabetic patients with add on teneligliptin

Add-on therapy with teneligliptinis found superior over conventional therapy in reducing plasma glucose concentration (fasting and postprandial) and HbA1c levels ($p<0.05$) in patients with T2DM.

Study II: Diabetic patients having dyslipidemia.

Add- on therapy with teneligliptinis found better option over conventional therapy in terms of significant reduction inglycaemic as well as lipid profile.

Study III: Diabetic patients having hypertension

Add- on therapy with teneligliptinis found superior over conventional therapy in terms of significant reduction ofglycaemic parameters. Blood pressure was also improved in patients with concomitant hypertension.

Study IV: Diabetic patients having dyslipidemia and hypertension

Tenligliptin add on treatment with atorvastatin and telmisartanis found effective along-with conventional-therapy in terms of significant reducing hyperglycaemia. Lipid profile and blood pressure was also improvedin diabetic patients having dyslipidemia and hypertension.

Additionally, we also found significant rise in serum adiponectin levels inteneligliptintreated patients as compared to conventional therapy in study I, II, III and IV. However, due to co-morbid conditions,in study IV,we have not achieved any significant findings in lowering of lipid and blood pressure that could be because of progressive destruction of Beta cells. Thus required to start early stage combination therapy in patients to protect Beta cells which leads to improve the disease conditions.

i. Copies of papers published and a list of all publications arising from the thesis:

Paper published	
1.	***Parmar V**, Goswami S. Efficacy and safety of teneligliptin as add-on therapy to conventional therapy in indian patients with type 2 diabetes mellitus. Asian J Pharm Clin Res. 2019;12:12:116-120.*
2.	***Vinendra MP**, Sunita SG (2020) Efficacy and Safety of Teneligliptin as Add on Therapy in Indian Type 2 Diabetes Mellitus Patients having Dyslipidemia. J Diabetes Metab. 10:844. doi: 10.35248/2155-6156.20.11.844*
Paper Presented	
1.	E-Oral poster presentation titled "**Efficacy and safety of teneligliptin as add on therapy Indian type 2 diabetes mellitus patients having hypertension**" in prize session of ISCOMS (International Student Congress Of bio Medical Sciences) on 8th - 10th June 2021., Groningen, The Netherlands.
2.	Power point presentation on **"Efficacy and safety of teneligliptin as add on therapy Indian type 2 diabetes mellitus patients having dyslipidemia"** at DIACON 2019 international conference held on 27-29th sep. 2019. Ahmedabad., Gujarat
3.	Power point presentation on **"Efficacy and safety of teneligliptin as add on therapy to glimepiride/metformin in Indian patients with type 2 diabetes mellitus"** (Paper ID: PCP007) at GTUICON 2019 international conference., Gandhinagar, Gujarat

j. Patents (if any):

NA

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