

Efficacy and safety of teneligliptin, a novel dipeptidyl peptidase-4 inhibitor, in Korean patients with type 2 diabetes mellitus: a 24-week multicentre, randomized, double-blind, placebo-controlled phase III trial

We assessed the 24-week efficacy and safety of teneligliptin, a novel dipeptidyl peptidase-4 inhibitor, in Korean patients with type 2 diabetes mellitus (T2DM) that was inadequately controlled with diet and exercise. The present study was designed as a multicentre, randomized, double-blind, placebo-controlled, parallel-group, phase III study. Patients ($n = 142$) were randomized 2 : 1 into two different treatment groups as follows: 99 received teneligliptin (20 mg) and 43 received placebo. The primary endpoint was change in glycated haemoglobin (HbA1c) level from baseline to week 24. Teneligliptin significantly reduced the HbA1c level from baseline compared with placebo after 24 weeks. At week 24, the differences between changes in HbA1c and fasting plasma glucose (FBG) in the teneligliptin and placebo groups were -0.94% [least-squares (LS) mean -1.22 , -0.65] and -1.21 mmol/l (-1.72 , -0.70), respectively (all $p < 0.001$). The incidence of hypoglycaemia and adverse events were not significantly different between the two groups. This phase III, randomized, placebo-controlled study provides evidence of the safety and efficacy of 24 weeks of treatment with teneligliptin as a monotherapy in Korean patients with T2DM.

Keywords: antidiabetic drug, DPP-IV inhibitor, phase III study, type 2 diabetes

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Introduction

Teneligliptin is a novel dipeptidyl peptidase-4 (DPP-4) inhibitor belonging to the relatively novel pharmacological class of antihyperglycaemic agents that are now recommended as second- or first-line agents in specific situations [1–3]. In a phase II clinical trial, a 4-week course of teneligliptin (20 mg) monotherapy produced significant least squares (LS) mean reductions of -2.78 ± 0.43 , -1.93 ± 0.51 , and -2.08 ± 0.42 mmol/l in 2-h postprandial glucose level after breakfast, lunch and dinner, respectively, in Japanese patients with type 2 diabetes (T2DM) [4]. We therefore conducted the present phase III, randomized, double-blind, placebo-controlled study to assess the clinical efficacy and safety of teneligliptin in Korean patients with T2DM that was inadequately controlled with diet and exercise.

Methods

The present study was designed to confirm the efficacy and safety of teneligliptin compared with placebo. The study was

conducted in accordance with the principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies.

Participants considered eligible for the study were patients aged ≥ 18 years with T2DM inadequately controlled [glycated haemoglobin (HbA1c) $\geq 7.0\%$ and $< 10.0\%$] through diet and exercise for ≥ 8 weeks, who had not taken an oral antihyperglycemic agent (OHA) for ≥ 8 weeks. Exclusion criteria included current or history of significant comorbidities such as cardiovascular, hepatic or renal disease. Patients with adequate compliance ($\geq 80\%$) after a 2-week single-blind placebo run-in period underwent baseline evaluation and were randomized according to HbA1c (using an 8.0% threshold) into two parallel groups (teneligliptin and placebo; 2 : 1 matching) for 24 weeks.

The primary endpoint was change in HbA1c level from baseline to week 24. Secondary endpoints included HbA1c response to targets (HbA1c < 7 and $< 6.5\%$), changes in fasting plasma glucose (FPG), and homeostatic model assessment of insulin resistance (HOMA-IR) and β -cell function (HOMA- β) at week 24. Safety and tolerability were evaluated throughout the study. During the study, subjects who did not meet progressively stricter glycaemic goals immediately stopped the study without rescue therapy and underwent the evaluation planned for the final visit. These subjects were included in our analysis.

Three-way analysis of variance (ANOVA) was used to compare the primary endpoint between the treatment groups with baseline HbA1c and previous antihyperglycaemic agents as fixed effects. For other endpoints (FPG, HOMA- β and HOMA-IR),

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Table 1. Effects of teneligliptin and placebo on glucose metabolism between baseline and week 24.

	Teneligliptin	Placebo	Difference (95% CI)	p
HbA1c (%)				
<i>Baseline</i>				
Mean \pm s.d.	7.63 \pm 0.69	7.77 \pm 0.81		
<i>At week 24</i>				
Mean \pm s.d.	6.83 \pm 0.92	7.86 \pm 1.10		
<i>Change from baseline to week 24</i>				
Mean \pm s.d.	-0.81 \pm 0.80	0.09 \pm 0.75		
LS mean \pm s.e.	-0.90 \pm 0.09	0.03 \pm 0.12	-0.94(-1.22, -0.65)	<0.0001*
FPG, mmol/l				
<i>Baseline</i>				
Mean \pm s.d.	8.62 \pm 1.60	8.96 \pm 2.22		
<i>At week 24</i>				
Mean \pm s.d.	7.51 \pm 1.56	8.96 \pm 2.29		
<i>Change from baseline to week 24</i>				
Mean \pm s.d.	-1.11 \pm 1.35	0.00 \pm 1.85		
LS mean \pm s.e.	-1.08 \pm 0.16	0.13 \pm 0.22	-1.21 (-1.72, -0.70)	<0.0001†
HOMA-β, %				
<i>Baseline</i>				
Mean \pm s.d.	36.24 \pm 27.03	30.91 \pm 17.57		
<i>At week 24</i>				
Mean \pm s.d.	45.05 \pm 29.89	28.33 \pm 18.50		
<i>Change from baseline to week 24</i>				
Mean \pm s.d.	8.81 \pm 18.85	-2.58 \pm 14.99		
LS mean \pm s.e.	8.90 \pm 2.03	-3.33 \pm 2.75	12.23(5.78, 18.67)	0.0003†
HOMA-IR				
<i>Baseline</i>				
Mean \pm s.d.	3.58 \pm 3.87	3.25 \pm 2.79		
<i>At week 24</i>				
Mean \pm s.d.	2.84 \pm 2.39	2.93 \pm 2.12		
<i>Change from baseline to week 24</i>				
Mean \pm s.d.	-0.74 \pm 2.44	-0.32 \pm 1.69		
LS mean \pm s.e.	-0.64 \pm 0.17	-0.40 \pm 0.22	-0.24(-0.76, 0.28)	0.3611†

CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HOMA- β , homeostatic model assessment of β -cell function; HOMA-IR, homeostatic model assessment of insulin resistance; s.d., standard deviation; s.e., standard error; LS, least squares.

*Three-way analysis of variance.

†Analysis of covariance.

analysis of covariance was used with previous antihyperglycaemic agents as fixed effects and baseline HbA1c as a covariate. The differences between the parallel groups were calculated as LS means \pm standard error (s.e.). Responder rate (HbA1c <6.5%, HbA1c <7.0%) was analysed using multiple logistic regression analysis with the same factors as used in the three-way ANOVA. Two-sided p values <0.05 were considered significant. All statistical analyses were conducted using SAS version 9.2.

Results

Of the 222 subjects screened, 142 eligible subjects were randomized to treatment as follows: 99 received teneligliptin and 43 received placebo. In total, 122 subjects (86%) completed 24 weeks of treatment. Our analysis set consisted of 141 subjects for whom baseline and post-baseline values of the primary efficacy endpoint were available (Figure S1, File S1). The treatment groups were not significantly different with respect to demographic or clinical characteristics (Table S1, File S1). The mean

baseline HbA1c value was 7.63% in the teneligliptin group and 7.77% in the placebo group.

The changes in HbA1c from baseline to week 24 in the teneligliptin and placebo groups were LS mean \pm s.e. $-0.90 \pm 0.09\%$ and $0.03 \pm 0.12\%$, respectively (p < 0.001; Table 1). A greater decrease in HbA1c was observed with teneligliptin compared with placebo at week 8, which was sustained throughout the randomized treatment period (Figure 1). Significantly more subjects in the teneligliptin group achieved an HbA1c level of <7% at week 24 than in the placebo group (69.39% in the teneligliptin group vs 20.93% in the placebo group; p < 0.001; Figure S2, File S1). Approximately 34.69% of all subjects in the teneligliptin group achieved an HbA1c level <6.5% at week 24, whereas only 4.65% achieved this level in the placebo group (p = 0.0016; Figure S2, File S1). In subgroup analysis of subjects with high or low HbA1c level (≥ 8.0 or <8.0%) at baseline, the effect of teneligliptin was greater in the HbA1c $\geq 8.0\%$ group ($-1.15 \pm 0.99\%$, n = 25) than in the HbA1c <8.0% group ($-0.69 \pm 0.70\%$, n = 73; p = 0.0019).

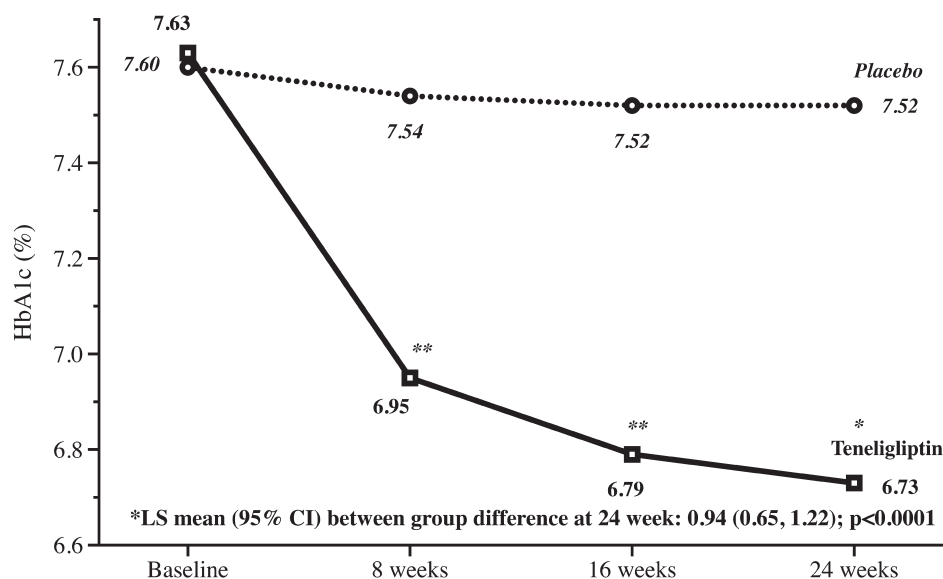


Figure 1. Changes in mean glycated haemoglobin (HbA1c) level from baseline. *According to three-way analysis of variance (ANOVA). ** $p < 0.0001$ versus placebo according to three-way ANOVA. CI, confidence interval; LS, least squares.

Teneligliptin decreased the FPG level from baseline to week 24, while the FPG level did not change in the placebo group. At week 24, the difference in change in FPG between the two groups was -1.21 mmol/l [95% confidence interval (CI) -1.72 , -0.70 ; $p < 0.0001$ (Table 1)].

β -cell function, as assessed by HOMA- β , was improved in the teneligliptin group at week 24 but not in the placebo group. At week 24, the difference in HOMA- β change between the groups was 12.23% [95% CI 5.78, 18.67; $p = 0.0003$ (Table 1)]. The teneligliptin group exhibited an improved HOMA- β score compared with the placebo group at week 8 and throughout the randomized treatment period (Figure S3, File S1). No significant difference in HOMA-IR was observed between the two treatment groups.

During this study, 81 adverse events (AEs) occurred in 49 (34.5%) of the 142 randomized subjects. Among the 81 AEs, 43 occurred in 29 (29.59%) teneligliptin-treated subjects, and 38 occurred in 20 (45.5%) placebo-treated subjects. The incidences of AEs were not significantly different between the two groups at week 24 ($p = 0.0660$). Hypoglycaemia occurred in one case in the placebo group but in no cases in the teneligliptin group.

Discussion

The results of the present study showed that 24 weeks of teneligliptin as a monotherapy was well tolerated and significantly decreased the HbA1c level in Korean patients with T2DM. This is the first 24-week, phase III, double-blind, randomized, placebo-controlled study on the efficacy and safety of teneligliptin.

At present, more than five competitive reversible inhibitors are currently on the market, and each has different characteristics. A Cochrane review that included 11 trials with sitagliptin and 14 trials with vildagliptin reported reductions in HbA1c level of $\sim 0.7\%$ and 0.6% , respectively, compared

with placebo [5]. Another DPP-4 inhibitor, saxagliptin, was also shown to reduce HbA1c by 0.45 – 0.63% compared with the placebo group [6]. In a recent phase II study with 12 weeks of teneligliptin treatment ($n = 324$), significant LS mean reductions in HbA1c for 10-, 20- and 40-mg groups vs a placebo group were -0.9% (95% CI -1.0 , -0.7), -0.9% (95% CI -1.1 , -0.7), and -1.0% (95% CI -1.2 , -0.9), respectively (all $p < 0.001$) [7]. Another recent study assessed the efficacy of teneligliptin when added to an ongoing metformin treatment at week 16, and the mean reductions in HbA1c and fasting plasma glucose level compared with placebo were -0.78% and -1.24 mmol/l, respectively [8]. The results of the present study in week 8 are consistent with these previous reports. Specifically, the differences in changes (baseline to week 8) in HbA1c and FPG between the teneligliptin 20-mg group and the placebo group were -0.80% (95% CI -1.02 , -0.59) and -0.95 mmol/l (95% CI -1.37 , -0.53), respectively (all $p < 0.001$). Moreover, the differences in HbA1c and FPG changes between the teneligliptin 20-mg group and the placebo group were maintained until week 24 [-0.94% (95% CI -1.22 , -0.65) and -1.21 mmol/l (95% CI -1.72 , -0.70), respectively (all $p < 0.001$)], and a large proportion (69.39%) of patients achieved an HbA1c level $< 7\%$ compared with those using other DPP-4 inhibitors ($\sim 40\%$) [9–11]. According to our results, teneligliptin has similar efficacy in the treatment of diabetes to other orally administered DPP-4 inhibitors.

β -cell destruction is key to the pathophysiology of T2DM, and β -cell conservation delays disease progression [12]. Improvements in β -cell function have been observed in clinical trials with the DPP-4 inhibitors sitagliptin, saxagliptin, vildagliptin, alogliptin and linagliptin [13–17]. Teneligliptin also resulted in increased HOMA- β index relative to placebo in the present study, suggesting that, like other DPP-4 inhibitors, teneligliptin modestly improves pancreatic function.

In the present study, the incidences of AEs and adverse drug reactions were not significantly different between the teneligliptin and placebo groups at week 24. Furthermore, no hypoglycaemic episodes were observed in the teneligliptin group. Together, these results indicate that teneligliptin is well tolerated and safe in Korean patients with diabetes.

In conclusion, this study showed that 20 mg of teneligliptin exhibits efficacy and safety after 24 weeks when administered once daily as a monotherapy to Korean patients with T2DM who are adhering to a diet and exercise control programme.

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Conflict of Interest

The authors have no conflicts of interest relevant to this article. S., C.-Y., K. A., C. H., B. J., H. C., C. W., M.-K., M. K., H. S., C. B., Y.-W. & S.-W. participated in designing the study and conducted the study and collected the data. S., C.-Y., & S.-W. analysed the data. S. and C.-Y. wrote the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

[File S1.](#) Supplementary method and result.

[Figure S1.](#) Study flow chart and patient dispositions.

[Figure S2.](#) Percentage of responders with HbA1c <7.0 or <6.5% from baseline to week 24. * $p < 0.0001$ vs. placebo by multiple logistic regression analysis with adjustment for HbA1c (<8.0 or ≥ 8.0) and for anti-diabetic medication (prior to the study). ** $p < 0.05$ vs. placebo by multiple logistic regression analysis with adjustment for HbA1c (<8.0 or ≥ 8.0) and for anti-diabetic medication (prior to the study). *** $p < 0.005$ vs. placebo by multiple logistic regression analysis with adjustment for HbA1c (<8.0 or ≥ 8.0) and for anti-diabetic medication (prior to the study).

[Figure S3.](#) Changes in mean HOMA- β score throughout the randomized treatment period. * By ANCOVA. ** $p < 0.005$ vs. placebo by ANCOVA. *** $p < 0.05$ vs. placebo by ANCOVA.

[Table S1.](#) Baseline characteristics.

[Table S2](#) Effects of teneligliptin and placebo on weight, and lipid profiles between baseline and week 24.

References

- Kim KS, Kim SK, Sung KM, Cho YW, Park SW. Management of type 2 diabetes mellitus in older adults. *Diabetes Metab J* 2012; **36**: 336–344.
- Rodbard HW, Jellinger PS, Davidson JA et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract* 2009; **15**: 540–559.
- Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015; **38**: 140–149.
- Eto T, Inoue S, Kadowaki T. 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* 2012; **14**: 1040–1046.
- Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch CL. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2008; **2**: CD006739.
- Rosenstock J, Sankoh S, List JF. Glucose-lowering activity of the dipeptidyl peptidase-4 inhibitor saxagliptin in drug-naive patients with type 2 diabetes. *Diabetes Obes Metab* 2008; **10**: 376–386.
- Kadowaki T, Kondo K. Efficacy, safety and dose-response relationship of teneligliptin, a dipeptidyl peptidase-4 inhibitor, in Japanese patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2013; **15**: 810–818.
- Kim MK, Rhee EJ, Han KA et al. 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* 2015; **17**: 309–312.

9. Aschner P, Kipnes MS, Luceford JK, Sanchez M, Mickel C, Williams-Herman DE. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* 2006; **29**: 2632–2637.
10. Rosenstock J, Aguilar-Salinas C, Klein E, Nepal S, List J, Chen R. Effect of saxagliptin monotherapy in treatment-naive patients with type 2 diabetes. *Curr Med Res Opin* 2009; **25**: 2401–2411.
11. Pi-Sunyer FX, Schweizer A, Mills D, Dejager S. Efficacy and tolerability of vildagliptin monotherapy in drug-naive patients with type 2 diabetes. *Diabetes Res Clin Pract* 2007; **76**: 132–138.
12. Jung KY, Kim KM, Lim S. Therapeutic approaches for preserving or restoring pancreatic beta-cell function and mass. *Diabetes Metab J* 2014; **38**: 426–436.
13. Mari A, Scherbaum WA, Nilsson PM et al. Characterization of the influence of vildagliptin on model-assessed β -cell function in patients with type 2 diabetes and mild hyperglycemia. *J Clin Endocrinol Metab* 2008; **93**: 103–109.
14. D'Alessio DA, Denney AM, Hermiller LM et al. Treatment with the dipeptidyl peptidase-4 inhibitor vildagliptin improves fasting islet-cell function in subjects with type 2 diabetes. *J Clin Endocrinol Metab* 2009; **94**: 81–88.
15. Del Prato S, Barnett AH, Huisman H, Neubacher D, Woerle HJ, Dugi KA. Effect of linagliptin monotherapy on glycaemic control and markers of beta-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. *Diabetes Obes Metab* 2011; **13**: 258–267.
16. DeFronzo RA, Fleck PR, Wilson CA, Mekki Q. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes and inadequate glycemic control: a randomized, double-blind, placebo-controlled study. *Diabetes Care* 2008; **31**: 2315–2317.
17. Cernea S, Raz I. Therapy in the early stage: incretins. *Diabetes Care* 2011; **34**(Suppl. 2): S264–S271.