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ORIGINAL ARTICLE

Teneligliptin versus sitagliptin in Korean patients with type 2 diabetes inadequately controlled with metformin and glimepiride: A randomized, double-blind, non-inferiority trial

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Aim: To assess the efficacy and safety of add-on therapy with the dipeptidyl peptidase-4 inhibitor teneligliptin compared with sitagliptin in patients with type 2 diabetes (T2DM) inadequately controlled with metformin and glimepiride.

Materials and Methods: This was a phase 3, randomized, double-blind, non-inferiority study of adult Korean subjects with T2DM (n = 201), with HbA1c ranging from 7.0% to 11.0%, on stable doses of metformin plus glimepiride. Subjects were randomized in a 1:1 fashion to receive either oral teneligliptin 20 mg or sitagliptin 100 mg for 24 weeks. The primary endpoint was change from baseline in HbA1c.

Results: At baseline, mean age was 60.56 ± 9.41 years, body mass index was 25.23 ± 2.85 kg/m^2 and HbA1c was 8.11% ± 0.79%. At 24 weeks, both groups achieved significant reductions from baseline in HbA1c (teneligliptin, −1.03% ± 0.10% [$P < 0.0001$]; sitagliptin, −1.02% ± 0.10% [$P < 0.0001$]). The inter-group difference was −0.01% (95% confidence interval [CI]: −0.28, 0.26; $P = 0.9497$); the upper limit of the 95% CI was within the preset limit for non-inferiority (0.4%). There were no significant differences between groups in the proportion of patients achieving HbA1c targets, or changes from baseline in fasting plasma glucose, body weight or lipid levels at 24 weeks. Rates of adverse events (teneligliptin, n = 63 [61.76%]; sitagliptin, n = 61 [62.24%]; $P = 0.9442$) and hypoglycaemia (teneligliptin, n = 32 [31.37%]; sitagliptin, n = 28 [28.57%]; $P = 0.6656$) were similar.

Conclusion: Teneligliptin was non-inferior to sitagliptin in the context of triple therapy for T2DM and is an important option in this setting.

KEYWORDS

DPP-4 inhibitor, sitagliptin, teneligliptin, triple therapy, type 2 diabetes

Yonghyun Kim and Eun Seok Kang contributed equally to this study and the manuscript.

1 | INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a commonly used class of treatment for type 2 diabetes mellitus (T2DM). They work by increasing levels of active glucagon-like peptide-1 (GLP-1), thereby promoting insulin secretion, in a blood glucose-dependent manner, and hence decreasing glucose levels while minimizing the risk of hypoglycaemia.[1] DPP-4 inhibitors are recommended both in the guidelines of the Korean Diabetes Association[2] and in international guidelines.[3–5] Meta-analyses have suggested that DPP-4 inhibitors may be more potent in reducing HbA1c levels in Asian T2DM patients than in non-Asian patients.[6,7]

Teneligliptin is a novel DPP-4 inhibitor comprising a chemical structure of four consecutive heterocyclic rings and a phenyl ring.[8] A crystallographic study suggested that the key interaction between a phenyl ring on teneligliptin and the S2 extensive subsite of DPP-4 enhances the drug's potency and may increase its selectivity.[9]

Teneligliptin has proven clinical efficacy and safety in randomized trials of T2DM, both as monotherapy[10] and as dual therapy in combination with metformin,[11,12] a sulfonylurea (glimepiride)[13] or insulin.[14] Four of these studies were conducted in Asia; two were undertaken specifically in Korean patients. On the strength of these data, teneligliptin was included among the DPP-4 inhibitors recommended in Korean guidelines for the treatment of T2DM.[2]

The Korea National Health and Nutritional Examination Survey in 2013 to 2014 estimated that 4.8 million (13.7%) adults (≥30 years) had T2DM.[15] While the treatment rate was high, the glycaemic control rate of HbA1c < 7% was only 43.5% in the Korean T2DM population, and only 23.3% when the HbA1c target was lowered to <6.5%. In total, 44.8% of Korean T2DM patients were treated with two oral antidiabetic agents and 26.1% were treated with three or more oral antidiabetic agents.[16] These figures provide insight not only into the utilization of dual and triple combination therapy, but also the continued unmet need in controlling T2DM, which provided the impetus for this clinical trial.

In patients with inadequate glycaemic control on metformin plus a sulfonylurea, DPP-4 inhibitors are a rational add-on for triple therapy. They have a neutral profile with regard to body weight gain and hypoglycaemia risk, and may help to minimize potential exacerbation by co-administered sulfonylureas, which are associated with elevated risks of body weight gain and hypoglycaemia.[2] Triple oral therapy that includes a DPP-4 inhibitor has shown superior glycaemic control to dual therapy.[17,18]

The objective of this study was to compare the efficacy and safety of adding teneligliptin or another established DPP-4 inhibitor, sitagliptin, to metformin and glimepiride in Korean patients whose T2DM was inadequately controlled.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a phase 3, randomized, double-blind, active-controlled, non-inferiority study evaluating the efficacy and safety of teneligliptin versus sitagliptin administered for 24 weeks as add-on therapy to metformin plus glimepiride in patients with T2DM and inadequate glycaemic control. It was conducted at 25 institutions in Korea from April 2015 to July 2017.

Prior to initiation, the study was approved by the Korean Ministry of Food and Drug Safety and by the Institutional Review Board at each participating centre. It was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Korean GCP guidelines, and other applicable local regulations. All study subjects provided informed consent prior to inclusion. The trial was registered at ClinicalTrials.gov (NCT02567994).

2.2 | Eligibility

The study included male and female subjects with T2DM aged ≥19 years at screening. All had HbA1c levels of 7.0% to 11.0%, a body mass index (BMI) of 20.0 to 40.0 kg/m^2, and fasting plasma glucose (FPG) < 270 mg/dL. Eligible subjects had been treated with metformin (≥1000 mg/d) and glimepiride (≥ 4 mg/d) for at least 8 weeks prior to screening, and were undergoing diet and exercise therapy.

Patients were excluded if they met any of the following criteria: a history of type 1 or secondary diabetes mellitus; treatment with a DPP-4 inhibitor or GLP-1 analogue within 6 months prior to screening, or insulin treatment within 12 weeks prior to screening; taking body weight-loss drugs or having unstable body weight (change ≥5% in the past 6 months); poor nutritional status, weak condition or excessive alcohol intake (>21 units/week), as judged by the investigator; cardiac failure (New York Heart Association Class III-IV), congestive failure or arrhythmia requiring treatment; a history of myocardial infarction, unstable angina or coronary artery bypass surgery within 6 months prior to screening; diastolic blood pressure > 100 mm Hg and/or systolic blood pressure > 180 mm Hg; fasting triglyceride levels >600 mg/dL; a history of malignant tumour within the past 5 years; significant liver or renal disease; or ongoing treatment for hyperthyroidism or an abnormal thyroid-stimulating hormone level.

2.3 | Interventions

After screening, patients were treated with placebo in a single-blind manner during a 2-week run-in period. Those determined to be eligible for the study were randomized in a 1:1 ratio to either oral teneligliptin 20 mg – the maximum approved dose of teneligliptin in Korea – plus placebo matching sitagliptin, or oral sitagliptin 100 mg (plus placebo matching teneligliptin) for 24 weeks. Although the maximum approved dose of teneligliptin in Japan is 40 mg/d, the Korean regulatory agency (Ministry of Food and Drug Safety) granted marketing authorization of teneligliptin 20 mg/d in Korea. Assignment to either group was stratified based on the HbA1c level measured at the run-in visit (<8.0% or ≥8.0%). Randomization numbers were generated by an independent statistician for each institution using a stratified block randomization method and SAS (version 9.1 or above, SAS Institute, Cary, North Carolina) PROC PLAN procedure.

All subjects continued with metformin and glimepiride during the study. Metformin was maintained at the prestudy dose throughout. Glimepiride dose reduction to a minimum of 2 mg/d was allowed after study enrolment at the discretion of the investigator; it could be reduced to ≥2 mg/d in the case of repeated (≥3 times a week)

hypoglycaemia (plasma glucose level ≤ 70 mg/dL) or an event of symptomatic hypoglycaemia.

Any subjects with uncontrolled blood glucose during the study (defined as FPG > 270 mg/dL from baseline to week 4; FPG > 240 mg/dL from weeks 5 to 12; or FPG > 200 mg/dL from weeks 13 to 24) did not continue to the study end.

2.4 | Assessments

The primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment for the teneligliptin group versus the sitagliptin group.

Secondary efficacy endpoints, all assessed relative to baseline at week 24, were: the proportion of subjects achieving HbA1c < 7.0% or < 6.5%; change in FPG; change in body weight and BMI; changes in serum lipids (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides); changes in homeostasis model assessment of β-cell function (HOMA-β), homeostasis model assessment of insulin resistance (HOMA-IR), highly sensitive quantification of C-reactive protein (hsCRP), insulin, C-peptide and active GLP-1; changes in meal tolerance test (MTT) variables, specifically 2 hour postprandial glucose, insulin, C-peptide, active GLP-1, and area under the curve ($AUC_{0\text{-}2h}$) for glucose, insulin, C-peptide and active GLP-1; and changes in blood glucose levels as assessed by self-monitoring of blood glucose (SMBG).

Safety assessments included adverse events (AEs), incidence of hypoglycaemia, laboratory values, vital signs and physical examination results. AEs were coded based on the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. Hypoglycaemia was classified as severe (requiring help from other people for the administration of carbohydrates or glucagon), documented symptomatic (plasma glucose level ≤ 70 mg/dL with typical symptoms of hypoglycaemia) or asymptomatic (plasma glucose level ≤ 70 mg/dL without typical symptoms).

2.5 | Statistical analyses

The sample size was calculated based on a non-inferiority margin for change in HbA1c at 24 weeks of 0.4%, and a standard deviation (SD) of 0.9%. Based on these calculations, at least 80 subjects were required for 1:1 randomization and 80% power at the upper limit of a two-sided significance level of 5%. Assuming a drop-out rate of 20%, planned recruitment was set at 200 subjects.

Inter-group differences in baseline characteristics were assessed using t-test or Wilcoxon's rank sum test for continuous variables, and Pearson's chi-square test or Fisher's exact test for categorical variables.

For the primary endpoint, an analysis of covariance (ANCOVA) was conducted with baseline HbA1c as a covariate. If the ANCOVA results showed that the upper limit of the two-sided 95% confidence interval (CI) for the difference in least squares means was <0.4%, the non-inferiority of teneligliptin to sitagliptin was deemed to be established. A paired t-test or Wilcoxon's signed rank test was performed for intra-group change.

For the percentage of subjects achieving HbA1c < 7.0% or < 6.5% at 24 weeks, Pearson's chi-square test or Fisher's exact test was performed. For all other secondary efficacy endpoints, inter-group differences were assessed using ANCOVA conducted with baseline outcome as a covariate, and a paired t-test or Wilcoxon's signed rank test was performed for intra-group change. Inter-group differences in AEs and hypoglycaemia rates were analysed using Pearson's chi-square test or Fisher's exact test.

Missing values in efficacy analyses were imputed with the last available value, using the last observation carried forward (LOCF) approach.

Two-sided tests were performed at a significance level of 5%. Mean and SD were presented for continuous variables, and frequency and percentage were provided for categorical variables.

Efficacy was analysed primarily in the per protocol set (PPS) and safety was assessed in the safety set. The PPS was defined as all randomized subjects who received at least one dose of the investigational drug and had at least one HbA1c measurement after dosing, and who completed the study without major protocol deviations. The safety set included all subjects who received at least one dose of the investigational drug.

3 | RESULTS

3.1 | Patients

Of 290 subjects who were screened, 201 eligible individuals were randomized: 103 to teneligliptin and 98 to sitagliptin (intention-to-treat [ITT] set) (Figure 1). One subject in the teneligliptin group did not receive the study drug; the remaining 200 all received at least one dose and were included in the safety set (n = 102 in the teneligliptin group; n = 98 in the sitagliptin group).

Thirty-three subjects were subsequently excluded from the PPS for the following reasons: premature withdrawal (n = 22); violation of inclusion/exclusion criteria (n = 4); taking prohibited concomitant medication (n = 3); misuse of the investigational drug (n = 2); and dose modification of glimepiride/metformin (n = 2). The remaining 167 subjects were included in the PPS (teneligliptin group [n = 86]; sitagliptin group [n = 81]).

Patient characteristics at baseline were comparable between the two groups (Table 1), with no statistically significant inter-group differences. For patients in the ITT set, the mean age was 60.56 ± 9.41 years; 116 (57.71%) were male; mean BMI was 25.23 ± 2.85 kg/m^2; and mean HbA1c was 8.11% ± 0.79%.

3.2 | Efficacy

Changes in HbA1c from baseline to week 24 and changes over time in the PPS are shown in Table 2 and Figure 2, respectively. Significant changes in mean HbA1c from baseline after 24 weeks of treatment were achieved in both groups (teneligliptin, −1.03% ± 0.10% [P < 0.0001]; sitagliptin, −1.02% ± 0.10% [P < 0.0001]). The inter-group difference was −0.01% (95% CI: −0.28, 0.26; P = 0.9497). The upper limit of the two-sided 95% CI was within the preset limit for non-inferiority (0.4%), thus showing the non-inferiority of teneligliptin compared with sitagliptin in this population.

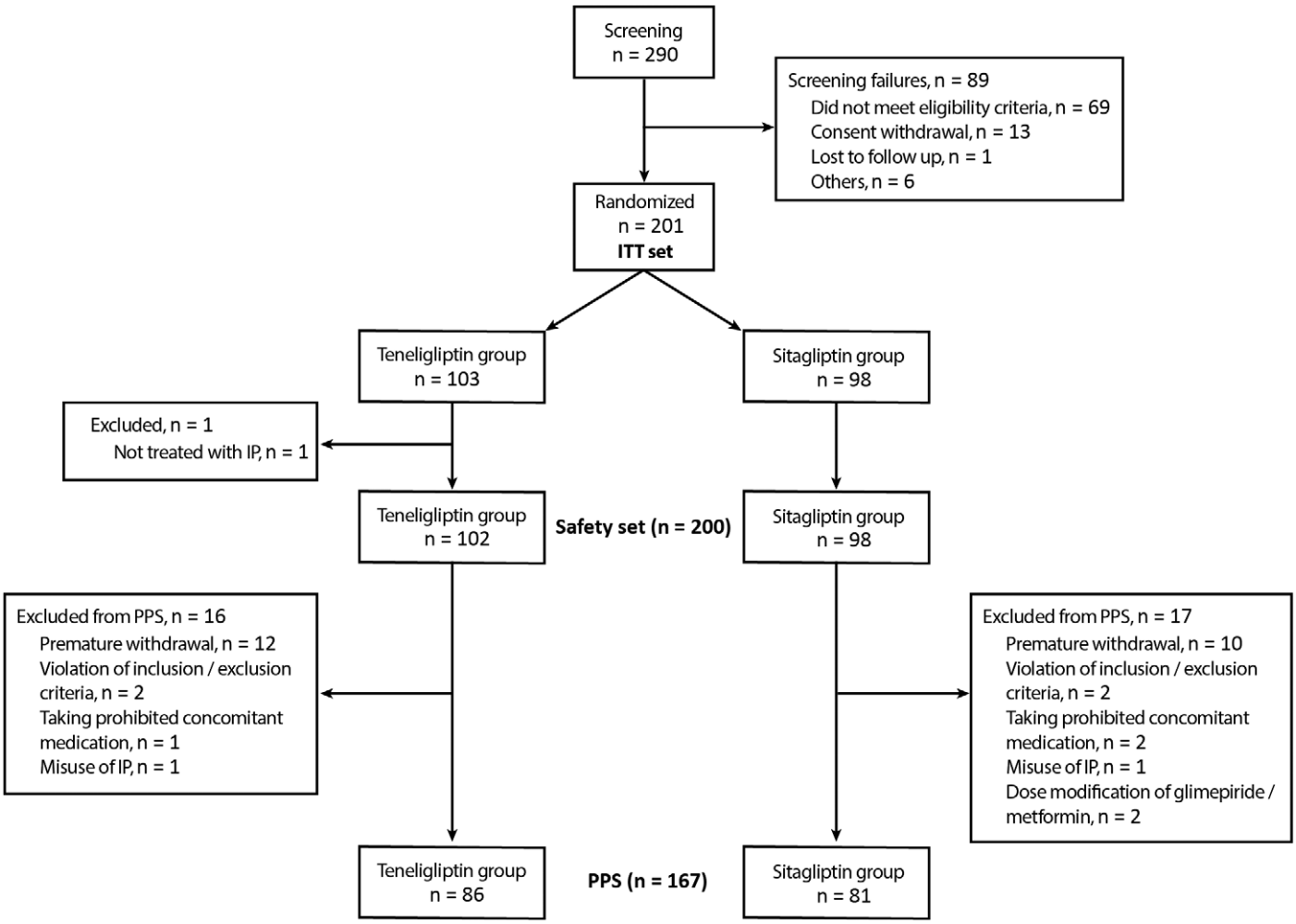

FIGURE 1 Subject disposition. IP, investigational product; ITT, intention to treat; PPS, per protocol set

The proportion of patients achieving HbA1c < 7.0% at week 24 was 50.00% (n = 43) in the teneligliptin group and 59.26% (n = 48) in the sitagliptin group. The proportion of patients achieving the more stringent goal of HbA1c < 6.5% was 29.07% (n = 25) with teneligliptin and 18.52% (n = 15) with sitagliptin. The inter-group differences of −9.26% and 10.55% for HbA1c < 7.0% and <6.5%, respectively, were not statistically significant (P = 0.2298 and P = 0.1103, respectively).

Significant reductions in FPG at week 24 were achieved in both groups: −12.00 ± 3.42 mg/dL in the teneligliptin group (P < 0.0001) and − 14.36 ± 3.53 mg/dL in the sitagliptin group (P = 0.0006) (Table 2).

The inter-group difference of 2.36 mg/dL (95% CI: −7.35, 12.06; P = 0.6322) was not statistically significant. Seven-point SMBG profiles also indicated significant reductions in blood glucose relative to baseline at week 24 in both groups.

Mean changes in body weight from baseline at week 24 were 0.17 ± 0.21 kg (P = 0.1973) in the teneligliptin group and 0.42 ± 0.22 kg (P = 0.0665) in the sitagliptin group. The inter-group difference of −0.26 kg (95% CI: −0.85, 0.34; P = 0.3934) was not statistically significant. Mean changes from baseline in BMI were 0.08 ± 0.08 kg/m^2 (P = 0.3154) with teneligliptin and 0.17 ± 0.08 kg/m^2 (P = 0.0385) with sitagliptin. Again, the inter-group difference of −0.10 kg (95% CI: −0.32, 0.12; P = 0.3898) was not statistically significant.

At week 24, there were no significant differences between the two groups in serum levels of total cholesterol, LDL-cholesterol, HDL-cholesterol or triglycerides (Table 2). Mean HOMA-β was increased from baseline at week 24 in both groups (teneligliptin, 14.24 ± 3.91 [μIU/mL] × [mmol/L]; sitagliptin, 8.84 ± 4.03 [μIU/mL] × [mmol/L]; P < 0.001 for each group). There were no significant differences between groups with regard to changes from baseline in HOMA-β, HOMA-IR, hsCRP, insulin or C-peptide. Mean changes from baseline in active GLP-1 at week 24 were 9.30 ± 1.15 pM in the teneligliptin group and 5.89 ± 1.19 pM in the sitagliptin group, with an inter-group difference of 3.41 pM (95% CI: 0.14, 6.68; P = 0.0408) that was statistically significant. There were no differences between groups in MTT variables at week 24 (Table 2).

3.3 | Safety

In the safety set, a total of 487 AEs were reported during the study in 124 subjects: 248 AEs in 63 subjects (61.76%) in the teneligliptin group and 239 AEs in 61 subjects (62.24%) in the sitagliptin group (P = 0.9442) (Table 3). All were mild or moderate in severity, except for one severe event of pulmonary congestion in the teneligliptin group, assessed as unlikely to be related to the investigational product.

Rates of adverse drug reactions for which a causal relationship to the investigational drug could not be ruled out were also similar

TABLE 1 Patient demographics

	Teneligliptin group n = 103	Sitagliptin group n = 98
Sex, n (%)		
Male	58 (56.31)	58 (59.18)
Female	45 (43.69)	40 (40.82)
Age (years), mean (SD)	60.70 (9.94)	60.41 (8.86)
Duration of diabetes (years), mean (SD)	13.01 (7.55)	12.70 (6.87)
Body weight (kg), mean (SD)	65.73 (10.65)	66.90 (10.22)
BMI (kg/m^2), mean (SD)	25.10 (2.88)	25.36 (2.84)
HbA1c (%), mean (SD)	8.14 (0.81)	8.08 (0.76)
FPG (mg/dL), mean (SD)	152.13 (32.76)	148.24 (33.74)
Diabetes complications, n (%)		
Retinopathy	18 (17.48)	15 (15.31)
Neuropathy	15 (14.56)	13 (13.27)
Vascular disorder	5 (4.85)	5 (5.10)
Nephropathy	0	4 (4.08)
Autonomic neuropathy	0	2 (2.04)
Diabetic foot	0	1 (1.02)

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; SD, standard deviation.
Intention-to-treat set.

between groups: 178 cases in 46 subjects (45.10%) in the teneligliptin group and 167 cases in 40 subjects (40.82%) in the sitagliptin group (P = 0.5409). Most were considered to be possibly or unlikely to be related to the investigational drug.

There were two serious AEs (SAEs) in two subjects (1.96%) in the teneligliptin group and three SAEs in three subjects (3.06%) in the sitagliptin group. AEs leading to treatment discontinuation were infrequent: two AEs in two subjects (1.96%) and one AE in one subject (1.02%) in the teneligliptin and sitagliptin groups, respectively (Table 3). AEs leading to discontinuation were assessed as not related or unlikely to be related to the investigational drug. No AEs resulted in death.

Hypoglycaemic episodes were experienced by 32 subjects (31.37%) in the teneligliptin group and 28 (28.57%) in the sitagliptin group (P = 0.6656). One subject in each group experienced an episode of severe hypoglycaemia. One subject in the sitagliptin group withdrew from the study because of repeated hypoglycaemic episodes.

There were no notable findings in clinical laboratory tests, vital signs or physical examination.

4 | DISCUSSION

This phase 3, double-blind, randomized trial showed the non-inferiority of teneligliptin to sitagliptin administered for 24 weeks as add-on therapy to metformin plus glimepiride in patients with T2DM and inadequate glycaemic control. Overall efficacy and safety profiles were similar between the two groups. The efficacy and safety of teneligliptin as monotherapy or part of dual combination therapy have been shown previously in a number of clinical trials, many of which were conducted in Asian patients.[10,11,13,14] However, the present work is the first phase 3 trial to assess teneligliptin as a component of triple therapy.

Teneligliptin differs from other clinically used DPP-4 inhibitors, including sitagliptin, with regard to its elimination pathway. With teneligliptin, this involves both hepatic and renal excretion,[8] whereas other DPP-4 inhibitors are typically eliminated by renal excretion only. The present demonstration of clinical non-inferiority provides evidence that this has no important bearing on overall efficacy and safety.

Although international and local guidelines all recommend lifestyle management as the mainstay of treatment for T2DM, with metformin as the preferred initial oral antihyperglycaemic agent in most patients, there remains no consensus regarding which classes of agent(s) to add as dual and triple therapy, if and when required.[2–5] DPP-4 inhibitors are an important option in these cases, but few phase 3 studies have directly compared DPP-4 inhibitors as add-on therapy.[19–22] This may be a particularly important exercise in Asian patients, because this population is characterized by less obesity and greater susceptibility to β-cell dysfunction than Western populations,[23,24] as well as differences in dietary behaviour that may warrant separate assessment of the efficacy of individual drugs. Reductions in mean HbA1c in the present study (teneligliptin, −1.03%; sitagliptin, −1.02%) were somewhat higher than those described in a recent meta-analysis assessing the impact of adding a DPP-4 inhibitor to dual therapy with metformin and a sulfonylurea (mean change in HbA1c: −0.71% [95% CI: −0.79, −0.63]).[18] This lends further support to the notion that DPP-4 inhibitors may be more potent in reducing HbA1c levels in Asian patients.[6,7]

In addition to HbA1c, there are of course other meaningful parameters in managing T2DM, and many were assessed in the present study. Importantly, no significant differences were found between teneligliptin and sitagliptin in lipid profiles or glycaemic variability. Both teneligliptin and sitagliptin improved insulin resistance, based on HOMA-β, which is in line with previous data showing the positive impact of teneligliptin on insulin resistance.[25]

In this study, the only significant difference between the two groups in any endpoint was a greater increase in active GLP-1 with the teneligliptin combination than with the sitagliptin combination. This may reflect the potency of teneligliptin as an inhibitor of DPP-4, based on its unique binding characteristics derived from its chemical structure.[9] To the best of our knowledge, this is a unique finding, representing the first time that a significant difference in GLP-1 increase has been shown in a direct comparison of DPP-4 inhibitors. Nevertheless, glycaemic control as measured by HbA1c was similar in both groups, which highlights an apparent discrepancy between a pharmacodynamic marker and clinical outcomes. DPP-4 inhibitors work indirectly to increase insulin blood levels through increasing the half-life of GLP-1. To achieve optimal glycaemic control, however, both increased blood levels of insulin as well as enhanced insulin sensitivity in the peripheral tissues are needed. We conclude that both teneligliptin and sitagliptin are effective DPP-4 inhibitors in humans to reach the expected pharmacologic action levels. Although the action of teneligliptin was stronger than that of sitagliptin, its clinical benefits may be limited beyond a certain saturation point.

In this study, levels of active GLP-1 in the blood were measured in the fasting state, but postprandial blood levels of active GLP-1

TABLE 2 Effects of teneligliptin versus sitagliptin on primary and secondary endpoints at 24 weeks

		Teneligliptin group n = 86	Sitagliptin group n = 81
HbA1c (%)			
Baseline	Mean (SD)	8.18 (0.81)	8.14 (0.78)
Change from baseline	LS mean (SE)	−1.03 (0.10)	−1.02 (0.10)
Inter-group difference	LS mean (95% CI)		−0.01 (−0.28, 0.26)
	P value		0.9497
FPG (mg/dL)			
Baseline	Mean (SD)	154.17 (32.62)	152.02 (33.83)
Change from baseline	LS mean (SE)	−12.00 (3.42)	−14.36 (3.53)
Inter-group difference	LS mean (95% CI)		2.36 (−7.35, 12.06)
	P value		0.6322
Body weight (kg)			
Baseline	Mean (SD)	65.02 (10.76)	66.73 (9.91)
Change from baseline	LS mean (SE)	0.17 (0.21)	0.42 (0.22)
Inter-group difference	LS mean (95% CI)		−0.26 (−0.85, 0.34)
	P value		0.3934
BMI (kg/m^2)			
Baseline	Mean (SD)	25.01 (2.78)	25.25 (2.74)
Change from baseline	LS mean (SE)	0.08 (0.08)	0.17 (0.08)
Inter-group difference	LS mean (95% CI)		−0.10 (−0.32, 0.12)
	P value		0.3898
Total cholesterol (mg/dL)			
Baseline	Mean (SD)	148.76 (29.48)	162.05 (38.40)
Change from baseline	LS mean (SE)	−1.26 (2.52)	−0.67 (2.60)
Inter-group difference	LS mean (95% CI)		−0.59 (−7.80, 6.62)
	P value		0.8714
LDL-cholesterol (mg/dL)			
Baseline	Mean (SD)	82.19 (24.71)	92.53 (34.38)
Change from baseline	LS mean (SE)	−1.32 (2.36)	1.48 (2.43)
Inter-group difference	LS mean (95% CI)		−2.80 (−9.53, 3.93)
	P value		0.4129
HDL-cholesterol (mg/dL)			
Baseline	Mean (SD)	48.21 (10.91)	46.68 (10.28)
Change from baseline	LS mean (SE)	0.31 (0.71)	0.75 (0.73)
Inter-group difference	LS mean (95% CI)		−0.44 (−2.46, 1.58)
	P value		0.6676
Triglyceride (mg/dL)			
Baseline	Mean (SD)	129.45 (76.75)	155.43 (87.54)
Change from baseline	LS mean (SE)	1.23 (6.70)	−10.41 (6.91)
Inter-group difference	LS mean (95% CI)		11.64 (−7.48, 30.76)
	P value		0.2311
HOMA-β ([μIU/mL] × [mmol/L])			
Baseline	Mean (SD)	45.74 (32.96)	61.27 (75.53)
Change from baseline	LS mean (SE)	14.24 (3.91)	8.84 (4.03)
Inter-group difference	LS mean (95% CI)		5.40 (−5.73, 16.53)
	P value		0.3395
HOMA-IR ([μIU/mL] × [mg/dL])			
Baseline	Mean (SD)	4.35 (4.84)	4.52 (4.89)
Change from baseline	LS mean (SE)	0.16 (0.28)	−0.56 (0.29)
Inter-group difference	LS mean (95% CI)		0.72 (−0.07, 1.51]
	P value		0.0733

TABLE 2 (Continued)

		Teneligliptin group n = 86	Sitagliptin group n = 81
hsCRP (mg/L)			
Baseline	Mean (SD)	1.96 (6.77)	0.85 (1.12)
Change from baseline	LS mean (SE)	−0.12 (0.26)	−0.17 (0.26)
Inter-group difference	LS mean (95% CI)		0.05 (−0.68, 0.77)
	P value		0.8996
Insulin (μIU/mL)			
Baseline	Mean (SD)	10.87 (9.45)	11.83 (10.44)
Change from baseline	LS mean (SE)	1.16 (0.53)	−0.28 (0.55)
Inter-group difference	LS mean (95% CI)		1.44 (−0.07, 2.95]
	P value		0.0607
C-peptide (ng/mL)			
Baseline	Mean (SD)	2.44 (1.69)	2.61 (1.63)
Change from baseline	LS mean (SE)	0.04 (0.10)	0.01 (0.10)
Inter-group difference	LS mean (95% CI)		0.03 (−0.25, 0.30)
	P value		0.8546
Active GLP-1 (pM)			
Baseline	Mean (SD)	5.24 (10.83)	5.29 (6.57)
Change from baseline	LS mean (SE)	9.30 (1.15)	5.89 (1.19)
Inter-group difference	LS mean (95% CI)		3.41 (0.14, 6.68)
	P value		0.0408

Abbreviations: BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, highly sensitive quantification of C-reactive protein; LS, least squares; SD, standard deviation; SE, standard error.
Per protocol set.

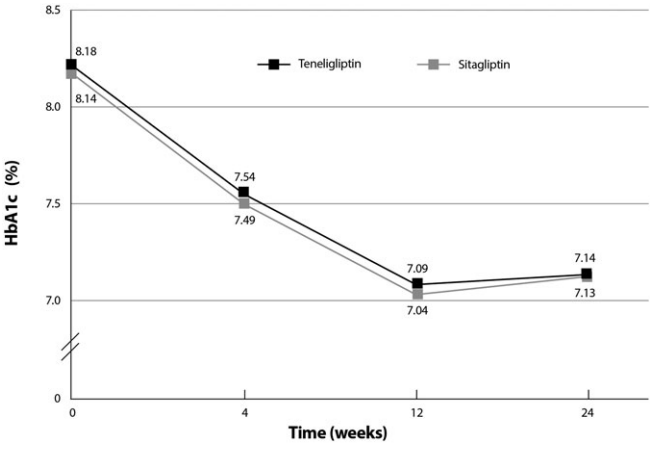

FIGURE 2 Timeline of changes in HbA1c level from baseline over the 24-week treatment period of the PPS

might have been a better marker of improvements in glycaemic control. HOMA-β was measured in the study before and after the addition of DPP-4 inhibitor, and significant increases were observed in both groups at week 24. This finding was meaningful because it showed improved insulin secretion because of the addition of a DPP-4 inhibitor to dual combination therapy.

Rates of hypoglycaemia were similar in both groups, and there was only one severe episode in each arm. Around 30% of patients (31.37% in the teneligliptin group and 28.75% in the sitagliptin group) in this study did experience any event of hypoglycaemia, with or without symptoms. Thus, it may be interpreted that adding

TABLE 3 Adverse events

	Teneligliptin (n = 102) n (%)	Sitagliptin (n = 98) n (%)	*P* value
Treatment-emergent AEs	63 (61.76)	61 (62.24)	0.9442
Adverse drug reactions[a]	46 (45.10)	40 (40.82)	0.5409
Serious AEs	2 (1.96)	3 (3.06)	0.6782
Discontinuations because of AEs	2 (1.96)	1 (1.02)	1.0000
Most common AEs[b]			
Hypoglycaemia	32 (31.37)	28 (28.57)	0.6656
Dizziness	8 (7.84)	9 (9.18)	
Asthenia	4 (3.92)	7 (7.14)	
Viral URTI	8 (7.84)	2 (2.04)	
Hunger	3 (2.94)	6 (6.12)	
Tremor	2 (1.96)	7 (7.14)	
Hyperhidrosis	1 (0.98)	6 (6.12)	

Abbreviations: AE, adverse event; URTI, upper respiratory tract infection.
Safety set.
[a] Assessed as certain, probable, possible or unlikely to be related to the investigational product, or not assessable/unclassified.
[b] Experienced by >5% of patients in either group.

teneligliptin to glimepiride may increase the risk of hypoglycaemia. However, without a placebo-controlled arm, we were unable to conclude whether the incidence of hypoglycaemia was truly increased. Furthermore, the absolute majority of hypoglycaemic events in this study were asymptomatic and non-serious. This suggests that neither drug greatly exacerbated the potential for

elevated risk of hypoglycaemia associated with sulfonylurea therapy, which is well documented.

Although a recent meta-analysis found a 50% increase in the risk of hypoglycaemia when a DPP-4 inhibitor was added to a sulfonylurea, compared with placebo added to a sulfonylurea,[26] in the present study, no patient in the teneligliptin group, and only one patient in the sitagliptin group, withdrew because of hypoglycaemia, and two more (also in the sitagliptin group) had glimepiride dose reductions to the permitted minimum of 2 mg/d (Figure 1). Hence, the data suggest that, as a component of triple therapy, teneligliptin isn't any more significantly associated with hypoglycaemia than sitagliptin. Teneligliptin can be as safely combined as sitagliptin with a sulfonylurea providing there is careful monitoring of glycaemic control and appropriate dose adjustments are applied, when needed. Prescription of triple therapy should be justified on the basis of prior response to medications and balancing between the potential risks versus benefits.

Neither teneligliptin nor sitagliptin significantly increased mean body weight; hence, neither appears to exacerbate the body weight gain often associated with sulfonylureas.[2]

The limitations of the study should be acknowledged. This trial was conducted in an Asian diabetic cohort with a mean BMI of 25 kg/m^2. As such, the results of this trial are not generalizable to other T2DM populations differing greatly in anthropometric parameters, demographics or ethnicity. For example, potential ethnic differences may be considered in interpreting the low incidences of symptomatic hypoglycaemia, but because this study was conducted in a homogeneous population, it was not possible to compare pharmacologic effects between ethnic groups.

In conclusion, as recent guidelines have stipulated, selection of a third agent as add-on therapy to metformin and sulfonylurea should be based on the individual patient's clinical characteristics as well as on efficacy, side effects, mechanism of action, risk of hypoglycaemia, effect on body weight, patient preference, and combined comorbidity.[27] In this setting, the first-ever direct, head-to-head, comparative clinical trial of two DPP-4 inhibitors, teneligliptin and sitagliptin, in an Asian T2DM population who were not controlled with dual metformin/sulfonylurea combination therapy, clearly showed that teneligliptin 20 mg met the primary endpoint of showing non-inferiority to sitagliptin 100 mg. There were no significant differences between teneligliptin and sitagliptin in all other evaluated efficacy and safety variables, thereby indicating that teneligliptin provides an important treatment option in this setting of difficult-to-treat T2DM.

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CONFLICTS OF INTEREST

JiYoung You and Se-Jin Kim are employees of Handok Inc. All the other authors have no conflicts of interest relevant to this article.

Author contributions

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