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BRIEF REPORT

Efficacy and safety of teneligliptin added to canagliflozin monotherapy in Japanese patients with type 2 diabetes mellitus: A multicentre, randomized, double-blind, placebo-controlled, parallel-group comparative study

Takashi Kadowaki MD, PhD[1] | Nobuya Inagaki MD, PhD[2] | Kazuoki Kondo MD, PhD[3] | Kenichi Nishimura MS[3] | Genki Kaneko MS[3] | Nobuko Maruyama Bachelor of Pharmacology[3] | Nobuhiro Nakanishi MMath[3] | Maki Gouda B.Sc.(Agr.)[3] | Hiroaki Iijima PhD[3] | Yumi Watanabe PhD[3]

[1]Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[2]Department of Diabetes, Endocrinology, and Nutrition, Graduate School of Medicine, Kyoto University, Kyoto, Japan

[3] Ikuyaku. Integrated Value Development Division, Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan

Correspondence
Yumi Watanabe, Medical Science Department, Ikuyaku. Integrated Value Development Division, Mitsubishi Tanabe Pharma Corporation, 17–10 Nihonbashi-Koamicho, Chuo-ku, Tokyo 103-8405, Japan.
Email: watanabe.yumi@mf.mt-pharma.co.jp

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Dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium glucose co-transporter 2 (SGLT2) inhibitors are frequently used in combination for the treatment of type 2 diabetes mellitus (T2DM). We examined the efficacy and safety of teneligliptin (a DPP-4 inhibitor) added to canagliflozin (an SGLT2 inhibitor) monotherapy in Japanese patients with poorly controlled T2DM as part of the development of a fixed-dose combination of teneligliptin and canagliflozin.

Japanese patients treated with canagliflozin (100 mg) for ≥12 weeks were randomized to receive add-on teneligliptin (20 mg; C + T group) or placebo (C + P group) for 24 weeks. The primary endpoint was change in glycated haemoglobin (HbA1c) from baseline to Week 24. The between-group differences in reductions from baseline to Week 24 were significantly greater in the C + T group for HbA1c (−0.94%; $P < .001$). The incidence of adverse events was similar in both groups (55.8% and 49.4% in the C + T and C + P groups, respectively). No episodes of hypoglycaemia were reported. Teneligliptin added to ongoing canagliflozin monotherapy improved glycaemic control and was well tolerated in Japanese patients with inadequately controlled T2DM.

KEYWORDS

canagliflozin, dipeptidyl peptidase-4 inhibitor, sodium glucose co-transporter 2 inhibitor, teneligliptin, type 2 diabetes mellitus

1 | INTRODUCTION

By inhibiting the degradation of glucagon-like peptide-1, dipeptidyl peptidase-4 (DPP-4) inhibitors promote insulin secretion and suppress glucagon secretion. Because the mode of action is dependent on the glucose concentration, DPP-4 inhibitors have a low risk of causing hypoglycaemia.[1] Sodium glucose co-transporter 2 (SGLT2) inhibitors reduce urinary glucose reabsorption by inhibiting SGLT2, lower plasma glucose in an insulin-independent manner and help to alleviate glucose toxicity. They are also expected to improve insulin resistance by alleviating glucose toxicity and decreasing body weight.[2,3] The independent mechanisms of action of these drugs and the low risk of hypoglycaemia provide support for combination therapy as a therapeutic option. Indeed, prior studies have demonstrated

that combination therapy with an SGLT2 inhibitor and a DPP-4 inhibitor was effective and well tolerated.[4–8]

Consequently, fixed-dose combinations of a DPP-4 inhibitor and an SGLT2 inhibitor are anticipated, and 2 fixed-dose combination drugs of a DPP-4 inhibitor and an SGLT2 inhibitor, linagliptin/empagliflozin and saxagliptin/dapagliflozin, have been launched in the USA and Europe, respectively.[8–10] No fixed-dose combinations of a DPP-4 inhibitor and an SGLT2 inhibitor have been approved in Japan.

In this context, the development of a fixed-dose combination of teneligliptin, a DPP-4 inhibitor, and canagliflozin, an SGLT2 inhibitor, has proceeded. A study examining the efficacy and safety of adding canagliflozin to ongoing teneligliptin therapy in Japanese patients has also been conducted (NCT02354235, NCT02220907), and the results have been reported previously.[11,12] In this study, we examined the efficacy of teneligliptin added to canagliflozin monotherapy in Japanese patients with poorly controlled T2DM as part of the development programme. This is the first clinical trial evaluating the efficacy and safety of adding a DPP-4 inhibitor to ongoing SGLT2 inhibitor treatment in Japanese T2DM patients. Therefore, this trial provides important information because there are differences in the pathology of T2DM between Japanese and Caucasian patients.[13]

2 | METHODS

Details of the patient inclusion/exclusion criteria, secondary efficacy endpoints and statistical analyses are provided in Appendix S1 (Methods). In brief, Japanese patients with T2DM and inadequate glycaemic control despite canagliflozin monotherapy in conjunction with diet and exercise therapy were eligible, provided they had undergone canagliflozin monotherapy for ≥8 weeks before the run-in period.

2.1 | Ethics

This trial complied with the Declaration of Helsinki, the Japanese Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices, Good Clinical Practice, and the approved study protocol. The procedures were approved by institutional review boards at all participating institutions, which are listed in Appendix S1. The trial was registered at ClinicalTrials.gov (NCT02354222).

2.2 | Study design and treatments

The study comprised a 4-week run-in period, a 24-week double-blind treatment period, and a 2-week post-treatment observation period (Figure S1). All patients received canagliflozin at a dose of 100 mg (the approved dose in Japan) once daily before breakfast during the run-in period, treatment period and post-treatment observation period. At the start of the treatment period, patients were randomized in a 1:1 manner to receive placebo (C + P group) or teneligliptin (C + T group) at a dose of 20 mg once daily before breakfast. Randomization was performed using the permuted block method. Diet and exercise therapy was to continue unchanged throughout the trial.

2.3 | Primary efficacy and safety endpoints

The primary efficacy endpoint was the change in HbA1c from baseline to the end of the treatment period. The safety of C + T and C + P was assessed in terms of adverse events (AEs), hypoglycaemia, laboratory variables (haematology, blood biochemistry and urinalysis), electrocardiography and vital signs. AEs were evaluated in terms of their seriousness and relationship to the study drugs. AEs and drug-related AEs were classified according to the System Organ Class and Preferred Term using the MedDRA version 18.1J.

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

A total of 213 patients were initially enrolled, of whom 59 discontinued before the treatment period (Figure S2); therefore, 154 patients were randomized, with 77 patients per group. Patient characteristics are shown in Table S1, Appendix S1.

3.2 | Efficacy variables

The primary endpoint, the LS mean ± SE (baseline value as covariate) change in HbA1c from baseline to Week 24 (LOCF) was 0.00% ± 0.08% and −0.94% ± 0.08% in the C + P and C + T groups, respectively, with a significant between-group difference of −0.94% ± 0.11% ($P < .001$, two-sided ANCOVA as specified in the protocol) (Table S2, Appendix S1). As illustrated in Figure 1, HbA1c started to decrease within 4 weeks of treatment in the C + T group and continued to decrease through to Week 12, and the reduction was sustained until the end of treatment. By contrast, HbA1c remained broadly unchanged in the C + P group. Significantly greater

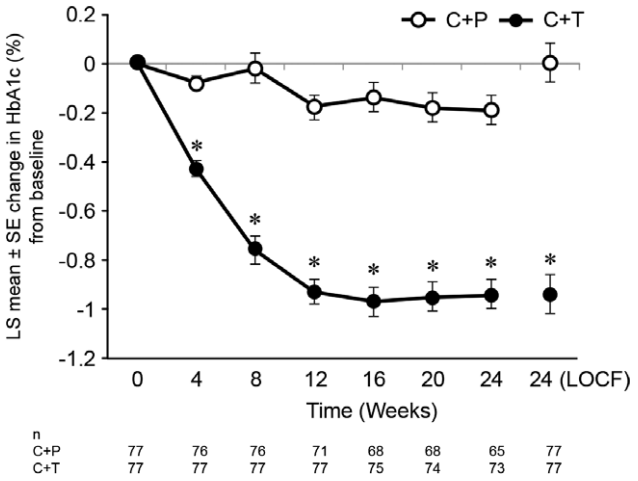

FIGURE 1 Changes in HbA1c from baseline to each visit during the 24-week treatment period, and at the last observation carried forward. Values are expressed as the least squares mean ± standard error. The least squares mean was determined by analysis of covariance with treatment group as a fixed factor and the baseline value as a covariate. *$P < .001$ for the C + T group vs C + P group at all time points. C + P, canagliflozin plus placebo; C + T, canagliflozin plus teneligliptin; HbA1c, glycated haemoglobin; LOCF, last observation carried forward; LS mean, least squares mean

proportions of patients in the C + T group than in the C + P group achieved HbA1c <7.0% (50.00% vs 8.11%, respectively; $P < .001$) or <8.0% (75.76% vs 18.42%, respectively; $P < .001$, 2-sided Fisher's exact test as specified in the protocol) at Week 24 (LOCF).

Table S2 (Appendix S1) shows the changes in other efficacy endpoints from baseline to Week 24 (LOCF). Supporting the change in HbA1c, the reduction in FPG was significantly greater in the C + T group, with a between-group difference of −15.6 ± 3.9 mg/dL (LS mean ± SE, $P < .001$, two-sided ANCOVA [baseline value as covariate] as specified in the protocol). The absolute and percent changes in body weight were 0.11 ± 0.20 kg and 0.09% ± 0.29%, respectively, in the C + T group vs −0.98 ± 0.20 kg and −1.34% ± 0.29%, respectively, in the C + P group. The between-group differences in changes in body weight were 1.09 ± 0.29 kg and 1.43% ± 0.41% (both $P < .001$), respectively. Additional efficacy results and the results of a mixed-meal tolerance test are included in Appendix S1 (Results).

3.3 | Safety

Table 1 shows the incidence of AEs, including AEs of special interest in both groups. AEs and drug-related AEs occurred in 49.4% and 14.3% of patients, respectively, in the C + P group and in 55.8% and 6.5% of patients, respectively, in the C + T group. Serious AEs occurred in 2.6% and 1.3% of patients in the C + P and C + T groups, respectively. There were no serious drug-related AEs in either group. AEs led to discontinuation and drug-related AEs led to discontinuation in 3.9% and 1.3% of patients, respectively, in the C + P group.

TABLE 1 Adverse events

	C + P		C + T	
	n	(%)	n	(%)
AEs	38	(49.4)	43	(55.8)
Drug-related AEs	11	(14.3)	5	(6.5)
Serious AEs	2	(2.6)	1	(1.3)
Serious drug-related AEs	0	(0.0)	0	(0.0)
AEs leading to discontinuation	3	(3.9)	0	(0.0)
Drug-related AEs leading to discontinuation	1	(1.3)	0	(0.0)
AEs of special interest				
Hypoglycaemia	0	(0.0)	0	(0.0)
Osmotic diuresis	1	(1.3)	1	(1.3)
Volume depletion	0	(0.0)	1	(1.3)
Vulvovaginal candidiasis	1	(5.3)[a]	0	(0.0)
Urinary tract infection	1	(1.3)	0	(0.0)
Blood ketone bodies increased	2	(2.6)	1	(1.3)
Hepatic function impairment	2	(2.6)	2	(2.6)
Skin and subcutaneous tissue disorders	4	(5.2)	8	(10.4)
Cardiovascular-related events	0	(0.0)	1	(1.3)
Malignant neoplasm	2	(2.6)	0	(0.0)
Gastrointestinal disorders	6	(7.8)	9	(11.7)

Abbreviations: C + P, canagliflozin plus placebo; C + T, canagliflozin plus teneligliptin; AE, adverse event.

[a] In females only (n = 19).

There were no AEs leading to treatment discontinuation in the C + T group. In terms of AEs of special interest, there were no episodes of hypoglycaemia in either group. Gastrointestinal disorders (11.7% vs 7.8%) and skin and subcutaneous tissue disorders (10.4% vs 5.2%) were more common in the C + T group than in the C + P group. Malignant neoplasms occurred in 2.6% of patients in the C + P group and in no patients in the C + T group. Other AEs of clinical relevance occurred in ≤2 patients in each group.

4 | DISCUSSION

This randomized, placebo-controlled, double-blind, multicentre trial examined the efficacy and safety of teneligliptin or placebo added to canagliflozin therapy for 24 weeks in Japanese patients with inadequately controlled T2DM. Teneligliptin was associated with significant improvements in glycaemic control, including HbA1c, FPG and postprandial plasma glucose, compared with placebo. Moreover, greater proportions of patients in the C + T group achieved HbA1c <7.0% or <8.0%. These improvements were consistent with those observed in earlier clinical trials in which teneligliptin was added to oral hypoglycaemic drugs other than SGLT2 inhibitors.[14–16] In fasting conditions, the fasting proinsulin/C-peptide ratio was reduced and HOMA2-%B was increased in the C + T group compared with the C + P group. In addition, in mixed-meal tolerance tests, there were reductions in the changes from baseline in postprandial plasma glucose, as well as increases in the change from baseline in C-peptide $AUC_{0\text{-}2h}$ and the C-peptide $AUC_{0\text{-}2hours}$/plasma glucose $AUC_{0\text{-}2hours}$ in the C + T group compared with the C + P group.

These findings seem reasonable considering the mechanism of action of DPP-4 inhibitors, which promote insulin secretion in a glucose concentration-dependent manner.[1] Taken together, these results support our hypothesis that teneligliptin added to ongoing canagliflozin therapy is beneficial in terms of improving glycaemic control in patients with inadequately controlled T2DM, because of their complementary but independent mechanisms of action.

Additionally, the use of canagliflozin and teneligliptin in combination is considered to have the following benefits. First, the attenuation of β-cell burden by the SGLT2 inhibitor may lead to enhanced incretin-stimulated insulin secretion. Second, because canagliflozin increases total GLP-1 after meals,[17] teneligliptin add-on therapy may increase the level of active GLP-1.

In this trial, the change in body weight from baseline to Week 24 was −0.98 kg in the C + P group and 0.11 kg in the C + T group. The change in urinary glucose/creatinine ratio from baseline was lower in the C + T group compared with the C + P group, probably because of the glucose-lowering effect of teneligliptin. This result suggests that calorie loss through glucose excretion was lower in the C + T group than in the C + P group throughout the treatment period. Furthermore, some meta-analyses and clinical trials of teneligliptin have reported that DPP-4 inhibitors negligibly increase body weight, probably as a result of enhanced insulin-stimulated glucose uptake.[15,16,18–20]

The present trial also examined the safety of teneligliptin added to ongoing canagliflozin therapy. Of note, there were no serious

drug-related AEs or deaths. Moreover, no episodes of hypoglycaemia were detected. AEs related to osmotic diuresis, volume depletion, increased serum ketone bodies, hepatic function impairment, skin disorders, cardiovascular disorders and gastrointestinal disorders were observed in the C + T group. Although skin disorders and gastrointestinal disorders were slightly more frequent in the C + T group, only one skin disorder (eczema) and one gastrointestinal disorder (constipation) were considered to be drug-related in the C + T group. These classes of AEs have already been reported for teneligliptin or canagliflozin, and there were no additional safety concerns. Overall, these findings suggest that teneligliptin added to canagliflozin therapy is likely to be well tolerated in clinical practice.

We previously reported that canagliflozin added to teneligliptin monotherapy in Japanese patients with poorly controlled T2DM was effective and well tolerated.[11,12] Taken together with the results of the present trial, this suggests that the fixed-dose combination of teneligliptin and canagliflozin may be a beneficial treatment option.

Some limitations of this study warrant mention. In particular, we enrolled only Japanese patients. However, data on the use of this drug combination in Japanese patients are important, particularly when we consider the differences in pathophysiology between Japanese and non-Japanese patients.[13] Longer studies may be needed to verify the current findings obtained over 24 weeks.

In conclusion, this trial showed that teneligliptin added to ongoing canagliflozin therapy was effective in terms of improving glycaemic control and was well tolerated in Japanese patients with inadequately controlled T2DM.

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Conflict of interest

T. K. has received consulting fees and/or speakers' bureau fees from Astellas Pharma Inc., AstraZeneca K.K., MSD K.K., Mitsubishi Tanabe Pharma Corporation, Novo Nordisk Pharma Ltd., Ono Pharmaceutical Co., Ltd., Sanofi K.K., Takeda Pharmaceutical Co., Ltd., Eli Lilly Japan K.K. and Nippon Boehringer Ingelheim Co., Ltd.; has received research support from Daiichi Sankyo Co., Ltd. and Takeda Pharmaceutical Co., Ltd.; has received scholarship grants from Astellas Pharma Inc., Daiichi Sankyo Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Sumitomo Dainippon Pharma Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Kissei Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Novo Nordisk Pharma Ltd., Sanofi K.K. and Ono Pharmaceutical Co., Ltd.; and teaches courses endowed by MSD K.K., Nippon Boehringer Ingelheim Co., Ltd., Novo Nordisk Pharma Ltd., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Kowa Pharmaceutical Co., Ltd. and Ono Pharmaceutical Co., Ltd. N. I. has received consulting fees and/or speakers' bureau fees from Astellas Pharma Inc., MSD K.K., Nippon Boehringer Ingelheim Co., Ltd., Sanofi K.K. and Takeda Pharmaceutical Co., Ltd.; has received research support from Eli Lilly Japan K.K., MSD K.K. and Mitsubishi Tanabe Pharma Corporation; and has received scholarship grants from Astellas Pharma Inc., AstraZeneca K.K., Daiichi Sankyo Co., Ltd., Japan Diabetes Foundation, Japan Tobacco Inc., Kissei Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., MSD K.K., Mitsubishi Tanabe Pharma Corporation, Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K.K., Novo Nordisk Pharma Ltd., Ono Pharmaceutical Co., Ltd., Pfizer Japan Inc., Sanwa Kagaku Kenkyusho Co., Ltd., Sanofi K.K., Sumitomo Dainippon Pharma Co., Ltd., Takeda Pharmaceutical Co., Ltd. and Taisho Pharmaceutical Co., Ltd. K. K., K. N., G. K., N. M., N. N., M. G., H. I. and Y. W. are employees of Mitsubishi Tanabe Pharma Corporation.

Author contributions

T. K., N. I. and K. K. supervised the design and protocol of the study and contributed to the interpretation and discussion of the results as medical advisors for this study. K. N., G. K. and N. M. contributed to the study design, and collected the data. N. N. contributed to the data processing and statistical analysis. M. G., H. I. and Y. W. contributed to the writing of the manuscript. All authors contributed to the discussion of data, reviewed the manuscript and approved the final version of the manuscript.

ORCID

Yumi Watanabe http://orcid.org/0000-0002-8875-7598

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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