


BRIEF REPORT

Efficacy and safety of canagliflozin as add-on therapy to a glucagon-like peptide-1 receptor agonist in Japanese patients with type 2 diabetes mellitus: A 52-week, open-label, phase IV study

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Funding information

The study was sponsored by Mitsubishi Tanabe Pharma Corporation.

Sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) are antihyperglycaemic agents with weight-lowering effects. The efficacy and safety of the SGLT2 inhibitor canagliflozin as add-on therapy in Japanese patients with type 2 diabetes mellitus (T2DM) and inadequate glycaemic control with a GLP-1RA (≥ 12 weeks) were evaluated in this phase IV study. Patients received canagliflozin 100 mg once daily for 52 weeks. Efficacy endpoints included change in glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), body weight, systolic blood pressure (SBP) and HDL cholesterol from baseline to week 52. Safety endpoints included adverse events (AEs), hypoglycaemia and laboratory tests. Of the 71 patients treated with canagliflozin, 63 completed the study. At 52 weeks, HbA1c was significantly reduced from baseline (-0.70% ; paired t test, $P < .001$). Significant changes were also observed in FPG (-34.7 mg/dL), body weight (-4.46%), SBP (-7.90 mm Hg), and HDL cholesterol (7.60% ; all $P < .001$). The incidence of AEs, adverse drug reactions and hypoglycaemia was 71.8%, 32.4% and 9.9%, respectively. All hypoglycaemic events were mild. These findings suggest that the long-term combination of canagliflozin with a GLP-1RA is effective and well tolerated in Japanese patients with T2DM.

KEYWORDS

canagliflozin, GLP-1 receptor agonist, phase IV, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Obesity is a cause of insulin resistance and can lead to the development and progression of type 2 diabetes mellitus (T2DM). While in Western countries body mass index (BMI) ≥ 30 kg/m² is considered the threshold for obesity, the Japan Society for the Study of Obesity defines it as a BMI ≥ 25 kg/m², as the incidence of obesity-associated chronic diseases, including T2DM, increases rapidly in patients with a BMI ≥ 25 kg/m² in Japan.¹ While the mean BMI in the Japanese general population has not increased over the past decade,² that of

patients with T2DM has gradually increased to ~ 25 kg/m²; therefore, the management of body weight in patients with T2DM has become an important issue.^{3,4}

In addition to their antihyperglycaemic effects, sodium-glucose co-transporter-2 (SGLT2) inhibitors reduce body weight through the caloric loss associated with increased urinary glucose excretion,⁵ while glucagon-like peptide-1 receptor agonists (GLP-1RAs) promote weight loss by decreasing appetite and delaying gastric emptying⁶; therefore, combination therapy with a GLP-1RA and an SGLT2 inhibitor can be suitable for patients with T2DM who are overweight or obese.

In non-Japanese patients with T2DM, this combination therapy resulted in improved glycaemic control and weight loss in randomized controlled trials.^{7,8} Although two long-term, open-label studies in Japanese patients with T2DM have been conducted, metabolic variables (body weight, blood pressure and lipid profile) warrant further investigation.^{9,10}

Type 2 diabetes is a risk factor for cardiovascular disease, and cardiovascular outcome studies investigating the use of SGLT2 inhibitors (EMPA-REG OUTCOME, CANVAS programme) and GLP-1RAs (LEADER, SUSTAIN-6) showed reduced risks of the composite endpoints of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.^{11,12} Furthermore, the CANVAS programme and a subanalysis of the EMPA-REG OUTCOME and LEADER trials suggested that SGLT2 inhibitors and GLP-1RAs have renal protective effects.¹² These data suggest that the combined use of SGLT2 inhibitors and GLP-1RAs is an optimal approach.

The aim of the present study was to investigate the long-term efficacy and safety of canagliflozin, an SGLT2 inhibitor, as add-on therapy in Japanese patients with T2DM inadequately controlled with the GLP-1RA liraglutide plus exercise and diet therapy.

2 | MATERIALS AND METHODS

Details of the patients' inclusion/exclusion criteria, sample size and statistical analyses are provided in the Supporting Information (File S2 Supplementary Methods). Briefly, Japanese patients with T2DM with inadequate glycaemic control despite receiving GLP-1RA monotherapy in conjunction with diet and exercise therapy were eligible.

2.1 | Ethics

This trial complied with the Declaration of Helsinki, 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 the institutional review boards at all participating institutions, which are listed in the Supporting Information (File S1). The trial was registered at ClinicalTrials.gov: NCT02227849.

2.2 | Trial design and treatment

This was a multicentre, non-randomized, uncontrolled, open-label post-marketing (phase IV) study conducted in Japan. The treatment period was 52 weeks, and all patients received liraglutide (constant dose 0.6 or 0.9 mg, the approved maximum dose in Japan) with diet and exercise therapy for ≥ 12 weeks prior to the treatment period, throughout the treatment period, and after the treatment period. Post-treatment follow-up lasted for 2 weeks from the day after the end of the treatment period or from the day after treatment discontinuation. During the treatment period, canagliflozin 100 mg was administered once daily before breakfast, based on the approved dosage and administration. There was no dose titration or adjustment.

2.3 | Outcomes

The major efficacy endpoints were: change in HbA1c and the proportions of patients with HbA1c $< 7\%$ (53 mmol/mol) and $< 8\%$

(64 mmol/mol); changes in fasting plasma glucose (FPG), body weight and blood pressure. Other efficacy endpoints are listed in the Supporting Information (Appendix S1 Supplementary Methods). Additionally, a systolic blood pressure (SBP)-stratified subgroup analysis of blood pressure was performed.

The specific safety endpoints were adverse events (AEs), hypoglycaemia, laboratory tests, 12-lead ECG and vital signs. Investigators and sub-investigators judged whether an AE was related to the study drug.

3 | RESULTS

3.1 | Patient flow and baseline characteristics

Of the 87 patients who granted consent, 16 withdrew before the treatment period, resulting in 71 patients entering the treatment period (File S3 and File S4).

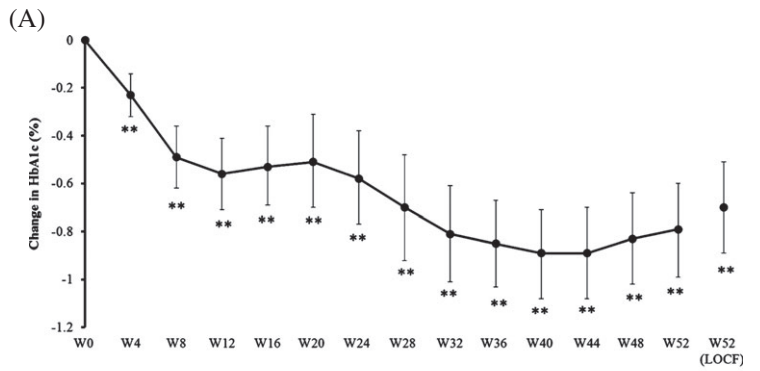
3.2 | Efficacy

Canagliflozin significantly reduced HbA1c at all time points ($P < .001$), with a mean change of -0.70% from baseline to week 52 (LOCF, 95% confidence interval [CI] $-0.89, -0.51$; Figure 1A). At week 52 (LOCF), the proportions of patients achieving an HbA1c $< 7.0\%$ (53 mmol/mol) and $< 8.0\%$ (64 mmol/mol) were 22.06% (95% CI 12.90, 33.76) and 44.44% (95% CI 27.94, 61.90), respectively. Similarly, FPG was significantly reduced at week 52 (LOCF; -34.7 mg/dL [95% CI $-43.7, -25.7$]) and at all time points (all $P < .001$; Figure 1B). The mean change in body weight at week 52 (LOCF) was -3.29 kg (95% CI $-3.85, -2.73$) or -4.46% (95% CI $-5.22, -3.69$; File S5 and Figure 1C). The mean change in SBP was -7.90 mm Hg (95% CI $-10.70, -5.10$; Figure 1D). In the sub-group analysis, SBP at baseline in the non-hypertensive group (SBP < 130 mm Hg, $n = 34$) was 120.46 mm Hg and the change from baseline at week 52 was -1.92 mm Hg, failing to show a significant change. The SBP at baseline in the hypertensive group (SBP ≥ 130 mm Hg, $n = 37$) was 139.52 mm Hg and the change from baseline at week 52 was -13.39 mm Hg, a significant decrease ($P < .001$). Additional efficacy results are included in the Supporting Information (Appendix S2, File S5 and S6).

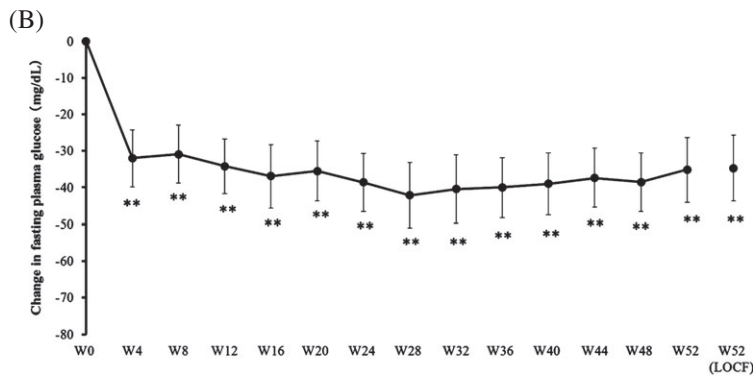
3.3 | Safety

Adverse drug reactions (ADRs)/AEs and ADRs occurred in 32.4% and 71.8% of patients, respectively (Table 1). Serious AEs occurred in 7.0% of patients. No serious ADRs occurred. AEs and ADRs that led to treatment discontinuation were reported in 5.6% and 1.4% of patients, respectively. There were no deaths.

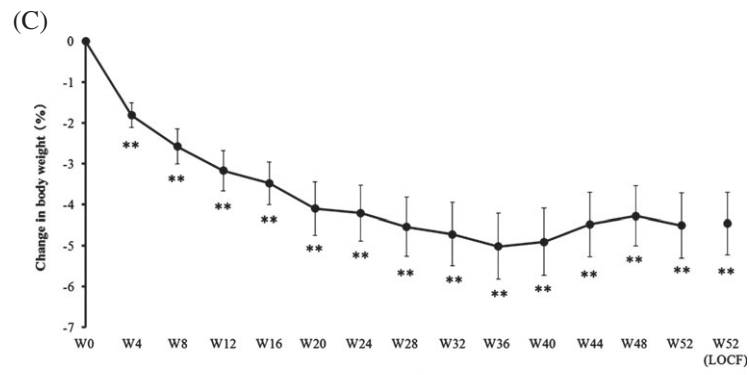
Hypoglycaemia occurred in 9.9% of patients (Table 1). All reported cases of hypoglycaemia were mild. The incidences of vulvovaginal candidiasis, osmotic diuresis and subcutaneous tissue disorders were 7.1%, 12.7% and 8.5%, respectively. The incidence rate of other AEs of special interest was $< 5.0\%$. Additional safety results are included in the Supporting Information (File S7 and S8).



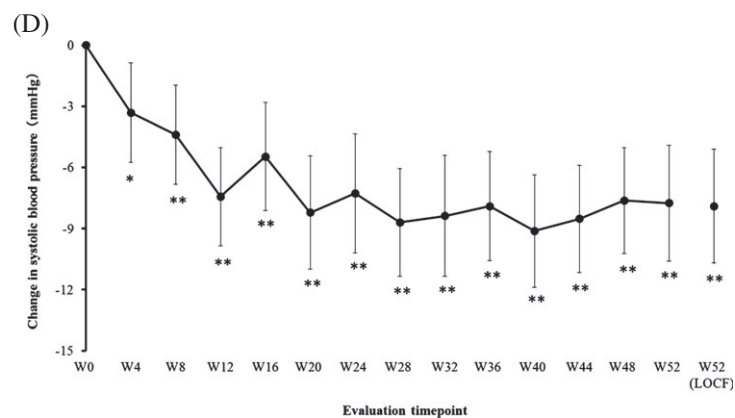
Week	W0	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	LOCF
N	71	70	70	69	69	66	66	66	65	63	63	63	63	63	71



Week	W0	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	LOCF
N	71	69	69	69	69	65	66	66	64	63	63	63	63	63	70



Week	W0	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	LOCF
N	71	69	69	69	69	65	66	66	64	63	63	63	63	63	70



Week	W0	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	LOCF
N	71	70	70	69	69	66	66	66	65	63	63	63	63	63	71

FIGURE 1 A, Change in glycosylated haemoglobin (HbA1c). B, Change in fasting plasma glucose. C, Percentage change in body weight. D, Change in systolic blood pressure over time (full analysis set). Data represent means \pm 95% confidence intervals. W0 = first day of the treatment period; WX = week X of the treatment period. *HbA1c (mmol/mol) = $10.93 \times \text{NGSP}(\%) - 23.52$. Plasma glucose conversion factor: 1 mg/dL = 0.0555 mmol/L. * $P < .01$; ** $P < .001$

TABLE 1 Summary of adverse events, adverse drug reactions and adverse events of special interest (safety analysis set)

	Canagliflozin 100 mg (N = 71)		
	n (%) ^a	Number of events	95% CI
AEs	51 (71.8)	169	59.9-81.9
ADRs	23 (32.4)	41	21.8-44.5
Serious AEs	5 (7.0)	5	2.3-15.7
Serious ADRs	0	0	0.0-5.1
AEs leading to discontinuation	4 (5.6)	4	1.6-13.8
ADRs leading to discontinuation	1 (1.4)	1	0.0-7.6
Death	0	0	0.0-5.1
Adverse events of special interest			
Hypoglycaemia	7 (9.9)	7	4.1-19.3
Urinary tract infection	1 (1.4)	1	-
Male genital infection	0 (0.0)	0	-
Vulvovaginal candidiasis ^b	2 (7.1) ²	2	-
Osmotic diuresis	9 (12.7)	15	-
Volume depletion	1 (1.4)	1	-
Fracture	1 (1.4)	1	-
Skin and subcutaneous tissue disorders	6 (8.5)	6	-
Malignant neoplasm	2 (2.8)	2	-
Cardiovascular-related events	0 (0.0)	0	-
Hepatic function impairment	0 (0.0)	0	-
Renal dysfunction	0 (0.0)	0	-

Abbreviations: ADR, adverse drug reaction; AE, adverse event; CI, confidence interval.

^a Number (%) of patients with incidents.

^b In women only.

4 | DISCUSSION

Among Japanese patients with T2DM inadequately controlled with a GLP-1RA plus exercise and diet therapy, add-on therapy with canagliflozin showed not only an antihyperglycaemic effect, but also a reduction in body weight and blood pressure. These effects were sustained without being diminished over the 52-week period. The degree of reduction in HbA1c, FPG levels and body weight was similar to that observed in previous trials of canagliflozin, administered alone or in combination with other antihyperglycaemic drugs.¹³⁻¹⁵ Moreover, SBP was markedly reduced, without an increase in pulse rate.

The GLP-1RA class of drugs improve glycaemic control by promoting insulin secretion and suppressing glucagon secretion.⁶ Furthermore, they reduce body weight by suppressing appetite and gastric emptying, reduce blood pressure, and improve patients' lipid profiles; however, they increase heart rate.⁶ SGLT2 inhibitors not only exert antihyperglycaemic effects, but can also reduce body weight by enhancing urinary glucose excretion.⁵ Additionally, they can reduce blood pressure and improve lipid profiles, and, unlike GLP-1RAs, they do not increase heart rate.⁵ In the present study, canagliflozin showed similar effects to its monotherapy, even after the effects of liraglutide stabilized; therefore, canagliflozin added

onto GLP-1RA monotherapy may have acted in a complementary manner.

Good glycaemic control, in addition to the control of body weight, blood pressure and lipids, is important in preventing the development of diabetes-related microangiopathy and macroangiopathy; however, goals for these variables may not be achieved in all patients.¹⁶ In the present study, along with antihyperglycaemic effects, beneficial effects on risk factors for complications were also observed. Canagliflozin reduced body weight in patients receiving a GLP-1RA for ≥ 12 weeks. It has been suggested that chronic glycosuria by SGLT2 inhibitors causes a compensatory increase in energy intake.¹⁷ In addition to effects on gastric emptying, GLP-1RAs also suppress appetite, resulting in weight loss from decreased food intake.⁶ Taken together, the beneficial effects on body weight in the present study, along with the differing mechanisms of the two drug classes, support the combined use of SGLT2 inhibitors and GLP-1RAs in patients with T2DM and obesity.

Significant reductions in blood pressure were observed in the present study; nevertheless, the baseline values of blood pressure were close to the therapeutic target for hypertension treatment in patients with T2DM in Japan ($< 130/80$ mm Hg). The possible mechanisms of the antihypertensive effects of SGLT2 inhibitors may be based on diuresis, body weight reduction, nephron remodelling and reduced arterial stiffness, but the exact mechanisms are not fully understood.¹⁸

Additionally, the present study found increased HDL cholesterol levels and decreases in triglyceride and serum uric acid levels (Supporting Information). These effects are generally known to contribute to a reduced risk of cardiovascular events.¹⁶ Moreover, the beneficial effects on fasting proinsulin/C-peptide ratio and updated homeostatic model assessment of β -cell function (HOMA2-%B) in this study (Supporting Information) suggest an improvement in pancreatic β -cell function. This may be attributable to the alleviation of glucose toxicity by the SGLT2 inhibitor and the reduced load on pancreatic β cells in insulin secretion.⁵ Taken together, combination therapy of an SGLT2 inhibitor and a GLP-1RA may provide additional clinical benefits compared with monotherapy with either GLP-1RAs or SGLT2 inhibitors.

With regard to safety, there were no serious ADRs or deaths, and $\sim 10\%$ of patients experienced hypoglycaemia. Other AEs of special interest observed in $\geq 5\%$ of patients during the study were vulvovaginal candidiasis, osmotic diuresis and skin and subcutaneous disorders. All these events were mild and did not lead to discontinuation. These findings are in line with other Japanese studies of canagliflozin therapy,¹³⁻¹⁵ and there were no additional safety concerns. Furthermore, in their joint position statement, the American Diabetes Association and European Association for the Study of Diabetes have urged caution in the use of combinations of multiple therapies because of issues relating to ADRs, drug interactions, patient adherence and increased costs.¹⁹ The cost burden of managing T2DM and obesity is increasing.^{20,21} While the cost of the combination therapy described in the present study is high, this may be offset by preventing the development of complications because of the improvement in risk factors. There is a clear need, however, for further cost-effectiveness studies.

The present study had a number of limitations, including its open-label nature and the fact that it was limited to Japanese patients, making generalization to other settings difficult. In addition, body composition was not evaluated in the present study; however, the reduction in waist circumference may suggest a decrease in visceral fat.

In summary, the present study indicates that long-term therapy with canagliflozin as add-on therapy to a GLP-1RA (52 weeks) is effective and well tolerated in Japanese patients with T2DM. It also suggests that combination therapy with an SGLT2 inhibitor and a GLP-1RA could be a useful therapeutic option for overweight and/or obese patients with T2DM. Recent clinical trials suggest that both SGLT2 inhibitors and GLP-1RAs have cardiovascular and renal protective effects¹²; therefore, combination therapy may also be a beneficial treatment option for patients with T2DM with multiple risk factors for complications. Additional studies in larger groups of patients are recommended to further explore these findings.

ACKNOWLEDGMENTS

The authors would like to thank Helen Robertson, Dr Sarah Williams and Emma Donadieu, MSc, of Edanz Medical Writing, for providing medical writing services on behalf of inScience Communications, Springer Healthcare. We would also like to thank Simone Boniface, of inScience Communications, Springer Healthcare, who edited the manuscript and styled it for submission. This medical writing assistance was funded by Mitsubishi-Tanabe Pharma Corporation.

Conflict of interest

S.H. has received consulting fees and/or speakers' bureau fees from Eli Lilly Japan KK, Mitsubishi Tanabe Pharma Corp., MSD KK, Novo Nordisk Pharma Ltd and Sanofi KK. N.I. has received consulting fees and/or speakers' bureau fees from Astellas Pharma Inc., MSD KK, Nippon Boehringer Ingelheim Co., Ltd, Sanofi KK and Takeda Pharmaceutical Co., Ltd, research support from AstraZeneca KK, Daiichi Sankyo Co., Ltd, Eli Lilly Japan KK, MSD KK and Mitsubishi Tanabe Pharma Corp., and scholarship grants from Astellas Pharma Inc., AstraZeneca K.K., Daiichi Sankyo Co., Ltd., Japan Tobacco Inc., Kissei Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., MSD KK, Mitsubishi Tanabe Pharma Corp., Nippon Boehringer Ingelheim Co., Ltd, Novartis Pharma KK, Novo Nordisk Pharma Ltd, Ono Pharmaceutical Co., Ltd, Pfizer Japan Inc., Sanwa Kagaku Kenkyusho Co., Ltd, Sanofi KK, Sumitomo Dainippon Pharma Co., Ltd, Takeda Pharmaceutical Co., Ltd and Taisho Toyama Pharmaceutical Co., Ltd. K.K., N.M., M.O., Y.K. and Y.W. are employees of Mitsubishi Tanabe Pharma Corp.

Author contributions

S.H., N.I. and K.K. supervised the design and preparation of the study protocol and contributed to the interpretation and discussion of the results as medical advisors. M.O. and N.M. contributed to the study design and collected the data. Y.K. contributed to data processing

and statistical analysis. Y.W. contributed to the preparation of the manuscript. All authors contributed to data discussion and manuscript review and approved the final version of the manuscript.

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REFERENCES

1. Kanazawa M, Yoshiike N, Osaka T, Numba Y, Zimmet P, Inoue S. Criteria and classification of obesity in Japan and Asia-Oceania. *Asia Pac J Clin Nutr*. 2002;11(suppl 8):S732-S737.
2. Ministry of Health, Labour and Welfare. Summary Results of the National Health and Nutrition Survey Japan, 2012. 2015. Japanese. <http://www.mhlw.go.jp/file/04-Houdouhappyou-10904750-Kenkoukyoku-Gantaisakukenkoukoushinka/kekkaigaiyou.pdf>. Accessed May 4, 2017.
3. Japan Diabetes Clinical Data Management Study Group. 2014. Japanese. <http://jddm.jp/data/index-2013.html>. Accessed May 4, 2017.
4. Kushiya A, Yoshida Y, Kikuchi T, et al. Twenty-year trend of increasing obesity in young patients with poorly controlled type 2 diabetes at first diagnosis in urban Japan. *J Diabetes Investig*. 2013;27:540-545.
5. Seufert J. SGLT2 inhibitors - an insulin-independent therapeutic approach for treatment of type 2 diabetes: focus on canagliflozin. *Diabetes Metab Syndr Obes*. 2015;8:543-554.
6. Seufert J, Gallwitz B. The extra-pancreatic effects of GLP-1 receptor agonists: a focus on the cardiovascular, gastrointestinal and central nervous systems. *Diabetes Obes Metab*. 2014;16:673-688.
7. Fulcher G, Matthews DR, Perkovic V, et al. Efficacy and safety of canagliflozin when used in conjunction with incretin-mimetic therapy in patients with type 2 diabetes. *Diabetes Obes Metab*. 2016;18:82-91.
8. Friás JP, Guja C, Hardy E, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2016;4:1004-1016.
9. Kaku K, Maegawa H, Tanizawa Y, et al. Dapagliflozin as monotherapy or combination therapy in Japanese patients with type 2 diabetes: an Open-Label Study. *Diabetes Ther*. 2014;5:415-433.
10. Seino Y, Yabe D, Sasaki T, et al. SGLT2 inhibitor luseogliflozin added to glucagon-like peptide 1 receptor agonist liraglutide improves glycaemic control with bodyweight and fat mass reductions in Japanese patients with type 2 diabetes: a 52-week, open-label, single-arm study. *J Diabetes Investig*. 2018;9:332-340.
11. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644-657.
12. DeFronzo RA. Combination therapy with GLP-1 receptor agonist and SGLT2 inhibitor. *Diabetes Obes Metab*. 2017;19:1353-1362.
13. Inagaki N, Kondo K, Yoshinari T, Takahashi N, Susuta Y, Kuki H. Efficacy and safety of canagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled with diet and exercise: a 24-week, randomized, double-blind, placebo-controlled, phase III study. *Expert Opin Pharmacother*. 2014;15:1501-1515.
14. Inagaki N, Kondo K, Yoshinari T, Kuki H. Efficacy and safety of canagliflozin alone or as add-on to other oral antihyperglycemic drugs in Japanese patients with type 2 diabetes: A 52-week open-label study. *J Diabetes Investig*. 2015;6:210-218.
15. Inagaki N, Harashima SI, Kaku K, et al. Long-term efficacy and safety of canagliflozin in combination with insulin in Japanese patients with type 2 diabetes mellitus. *Diabetes Obes Metab*. 2018;20:812-820.
16. Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among

- people with diabetes, 1988-2010. *Diabetes Care*. 2013;36:2271-2279.
17. Ferrannini G, Hach T, Crowe S, Sanghvi A, Hall KD, Ferrannini E. Energy balance after sodium-glucose cotransporter 2 inhibition. *Diabetes Care*. 2015;38:1730-1735.
 18. Maliha G, Townsend RR. SGLT2 inhibitors: their potential reduction in blood pressure. *J Am Soc Hypertens*. 2015;9:48-53.
 19. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2012;55:1577-1596.
 20. American Diabetes Association. Economic costs of diabetes in the US in 2012. *Diabetes Care*. 2013;36:1033-1046.
 21. Garber AJ. Obesity and type 2 diabetes: which patients are at risk? *Diabetes Obes Metab*. 2012;14:399-408.

SUPPORTING INFORMATION

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

How to cite this article: Harashima S, Inagaki N, Kondo K, et al. Efficacy and safety of canagliflozin as add-on therapy to a glucagon-like peptide-1 receptor agonist in Japanese patients with type 2 diabetes mellitus: A 52-week, open-label, phase IV study. *Diabetes Obes Metab*. 2018;20:1770-1775. <https://doi.org/10.1111/dom.13267>