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# A randomized, placebo-controlled trial to assess the efficacy and safety of sitagliptin in Japanese patients with type 2 diabetes and inadequate glycaemic control on ipragliflozin

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## Abstract

**Aims:** To investigate the efficacy, safety and tolerability of sitagliptin 50 mg once daily added to ipragliflozin 50 mg once daily monotherapy in Japanese patients with type 2 diabetes (T2D).

**Materials and Methods:** Japanese patients with T2D and glycated haemoglobin (HbA1c) 7.0% to 10.0% while treated with ipragliflozin 50 mg once daily were randomized 1:1 to additional treatment with sitagliptin 50 mg once daily ($N = 70$) or matching placebo ($N = 71$) for 24 weeks. The primary efficacy endpoint was change in HbA1c at Week 24. Secondary efficacy endpoints were changes in 2-hour post-meal glucose (PMG), total PMG 0- to 2-hour area under the curve ($AUC_{0-2h}$), and fasting plasma glucose (FPG).

**Results:** Baseline characteristics were similar in the two groups (mean age 55.5 years, mean baseline HbA1c 8.0%). After 24 weeks, the addition of sitagliptin provided significantly greater reduction in HbA1c compared to placebo (least squares [LS] mean difference −0.83% [95% confidence interval −1.05, −0.62]; $P < 0.001$). Significant reductions were also observed in all secondary endpoints: LS mean differences from placebo in changes in 2-hour PMG, total PMG $AUC_{0-2h}$, and FPG were −42.5 mg/dL, −67.0 mg·h/dL and −11.2 mg/dL, respectively (all $P < 0.001$). The incidence of adverse events (AEs) overall and incidence of predefined AEs of clinical interest (symptomatic hypoglycaemia, urinary tract infection, genital infection, hypovolaemia and polyuria/pollakiuria) were similar in the two groups.

**Conclusions:** In Japanese patients with T2D, sitagliptin 50 mg once daily added to ipragliflozin 50 mg once daily monotherapy provided significant improvement in glycaemic control and was generally well tolerated. ClinicalTrials.gov: NCT02577016.

**KEYWORDS**
combination therapy, DPP-4 inhibitor, incretins, SGLT2 inhibitor

# 1 | INTRODUCTION

Guidelines for the treatment of type 2 diabetes (T2D)[1,2] recommend initiating pharmacotherapy with a single, oral hypoglycaemic agent (OHA) when glycaemic control is not sufficiently improved with diet and exercise alone. However, most patients eventually require additional therapy to achieve or maintain glycaemic control. International guidelines recommend metformin as the initial OHA, with selection of additional therapy based on patient preference and clinical characteristics.[1] In contrast, the Japanese guideline states that initial therapy should be selected based on an individual patient's clinical condition and pathophysiology.[2]

Dipeptidyl peptidase-4 (DPP-4) inhibitors stabilize the active forms of the incretin's glucagon-like peptide-1 and glucose-dependent insulinotropic peptide, both of which stimulate insulin release in a glucose-dependent manner. They therefore improve glycaemic control without an increased risk of hypoglycaemia.[3] It has been reported that DPP-4 inhibitors more effectively lower glycated haemoglobin (HbA1c) levels in Asian (including Japanese) populations with T2D, compared with non-Asian populations.[4] This difference may be related to population-specific pathophysiology of T2D. For example, relative to other populations, White patients are more likely to develop T2D as a result of insulin resistance associated with obesity, whereas in Japanese and other East Asian patients, T2D more often results from an impaired insulin secretion capacity, especially the early phase of insulin secretion.[5,6] Sitagliptin, a DPP-4 inhibitor, has been widely used for over 10 years and has a well-characterized safety and tolerability profile.[7] Further, long-term addition of sitagliptin to usual care did not increase the risk of major adverse cardiovascular events in a large study evaluating cardiovascular outcomes.[8]

Sodium-glucose co-transporter-2 (SGLT2) inhibitors, a relatively new class of OHA, reduce blood glucose independently of insulin action by inhibiting the renal reabsorption of glucose, thereby increasing glycosuria.[9,10] SGLT2 inhibitors also improve glycaemic control without increased risk of hypoglycaemia.[11] In addition, SGLT2 inhibitors have the benefit of promoting weight loss, primarily mediated via the energy loss resulting from glycosuria.[10] In several randomized, placebo-controlled clinical trials, the once-daily SGLT2 inhibitor ipragliflozin effectively decreased HbA1c, fasting plasma glucose (FPG), and body weight in Japanese patients with T2D, in a manner that was generally safe and well tolerated.[12–17]

Since ipragliflozin and sitagliptin have distinct mechanisms of action, it seems likely that their combination would provide additive glucose-lowering. Furthermore, the combination of these agents is not expected to increase risk of hypoglycaemia or weight gain, two undesirable effects associated with some other OHAs. Therefore, a phase III, randomized, placebo-controlled, double-blind clinical trial was conducted to assess the safety and efficacy of adding sitagliptin 50 mg once daily to treatment of Japanese patients with T2D who have inadequate glycaemic control on ipragliflozin 50 mg once daily monotherapy. This trial was designed to support the development of a fixed-dose combination of sitagliptin/ipragliflozin and the results are reported here.

# 2 | METHODS

## 2.1 | Study design

The study was a randomized, placebo-controlled, parallel-group, double-blind multicentre trial conducted in Japan (Supplemental Figure S1). The study included: a screening period of up to 2 weeks; a medication stabilization period of 8 weeks for patients requiring initiation/stabilization of ipragliflozin 50 mg once daily and/or discontinuation of other OHAs (Group A); a 2-week placebo run-in period for all patients (Groups A and B, see below); and a 24-week treatment period. After the placebo run-in, patients were randomized centrally, using an internet-based interactive response system, in a 1:1 ratio to receive either sitagliptin 50 mg once daily or matching placebo. Randomization was stratified by prior use of OHAs other than base treatment with an SGLT2 inhibitor. Treatment with ipragliflozin 50 mg once daily was continued throughout the study. Sitagliptin 50 mg once daily and ipragliflozin 50 mg once daily were chosen for this study because they are the clinical doses most commonly used in Japan.

Meal tolerance tests were carried out at Weeks 0 and 24, starting 30 minutes after administration of study treatment. At Week 0, all patients received ipragliflozin and placebo; at Week 24, each received ipragliflozin and either sitagliptin or placebo. Blood samples were drawn at 0, 0.5, 1 and 2 hour(s) after beginning the meal. The test meal contained approximately 500 kcal (60% carbohydrate, 15% protein, 25% fat).

The study (MK-0431J-842; Clinical Trials.gov: NCT02577016) was conducted at 27 trial centres (Appendix 1) in Japan between November 2015 and November 2016, in accordance with the principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. Informed consent was obtained from all study patients.

## 2.2 | Study population

At the screening visit, eligible patients were men and women, aged ≥20 years, with T2D treated with diet and exercise therapy and meeting one of the following treatment criteria: on a stable dose of an SGLT2 inhibitor for ≥4 weeks and, during the 8 weeks prior to screening, either not on another OHA with HbA1c ≥7.0% and ≤10.0%, or on any additional single or low-dose dual combination oral OHA therapy with HbA1c ≥6.5% and ≤9.0% (Group A); or on a stable dose (≥10 weeks) of ipragliflozin 50 mg once daily and not on any additional OHAs during the 8 weeks prior to screening with HbA1c ≥7.0% and ≤10.0% (Group B). Two weeks prior to randomization, patients met the following criteria: on diet and exercise therapy ≥6 weeks; OHAs except for ipragliflozin discontinued for ≥8 weeks; on a stable dose of ipragliflozin 50 mg once daily ≥10 weeks; HbA1c ≥7.0% and ≤10.0%; and FPG ≤230 mg/dL.

Patients were excluded from the study if they had type 1 diabetes or a history of ketoacidosis, unstable diabetic retinopathy, poorly controlled hypertension, significant cardiovascular disease, active liver

disease, renal disease or urological disorders, a history of malignancy or haematological disorders or if they had been treated with insulin or thiazolidinediones within 12 weeks prior to screening or with sitagliptin within 8 weeks prior to screening. Laboratory exclusion criteria included serum alanine aminotransferase or aspartate aminotransferase levels >2 times the upper limit of normal, C-peptide <0.6 ng/mL, estimated glomerular filtration rate <60 mL/min/1.73 m$^2$, haemoglobin <11 g/dL (male) or <10 g/dL (female), or thyroid-stimulating hormone outside the central laboratory normal range.

## 2.3 | Objectives and hypotheses

The primary study objectives were to assess the efficacy, safety and tolerability of the addition of sitagliptin 50 mg once daily compared with placebo in Japanese patients with inadequate glycaemic control on ipragliflozin monotherapy. The primary hypothesis was that addition of sitagliptin 50 mg once daily provides greater reduction in HbA1c as assessed by change at Week 24 compared with placebo. Secondary objectives were to compare the effects of sitagliptin with placebo on change in 2-hour post-meal glucose (PMG), total PMG 0- to 2-hour area under the curve (AUC$_{0-2h}$) and FPG at Week 24. A tertiary objective was to compare the proportion of patients with HbA1c <7.0% at Week 24.

## 2.4 | Safety evaluations

Safety endpoints included adverse events (AEs), standard laboratory test results (eg, electrolytes, liver and renal safety tests), lipid panel, vital signs (including systolic and diastolic blood pressure and pulse rate), body weight and ECG. Prespecified AEs of interest were symptomatic hypoglycaemia, urinary tract infection, genital infection, hypovolaemia and polyuria/pollakiuria.

## 2.5 | Statistical analyses

The population for efficacy analyses included all randomized patients who received at least one dose of study medication and who had ≥1 measurement (baseline or post-baseline) of the specific endpoint and had a baseline measurement if required. Safety analyses included all randomized patients who received ≥1 dose of study medication. All statistical tests were conducted at α = 0.05, two-sided.

The rate of compliance with study medication for each treatment population was calculated as the mean of the percentage of each patient's days of compliance with study medication ([Number of Compliant Days/Number of Days in the Treatment Period] × 100).

A longitudinal data analysis model[18] was used for the analysis of change from baseline in HbA1c. The model included terms for treatment, time, prior use of OHAs, and the interactions of treatment by time (categorical), time by prior use of OHAs (other than SGLT2 inhibitors) and treatment by time by prior use of OHAs, with a constraint

that the true mean at baseline is common to all treatment groups (which is valid due to randomization). The same model was used to analyse change from baseline in 2-hour PMG, total post-meal glucose AUC$_{0-2h}$, and FPG Week 24.

The proportion of patients who achieved HbA1c <7.0% at Week 24 was calculated by treatment group. Patients with missing HbA1c data at Week 24 were considered as not having achieved a level of <7.0%. To provide the adjusted odds ratio relative to placebo, the percentage of individuals at the HbA1c goal of <7.0% at Week 24 was analysed using a logistic regression model including terms for treatment and prior use of OHAs. Multiple imputations were carried out to impute missing data based on the longitudinal data analysis model used for analysis of HbA1c. The parameter estimates on the adjusted log odds ratio from the respective imputed datasets were combined using the asymptotic theory of Robins and Wang.[19] The log odds ratio was back transformed into odds ratio for final reporting.

Safety and tolerability were assessed by clinical review of all relevant variables, including AEs, laboratory tests, ECG, vital signs and body weight, during the treatment period and for 14 days after treatment ended. For AE summary, including any AE, any drug-related AE, any serious AE, any serious drug-related AE and discontinuation due to an AE, and for specific AEs and laboratory tests exceeding predetermined limits of change (PDLC) with incidence ≥4 patients in either treatment group, between-group comparison point estimates with 95% confidence intervals (CIs) were calculated using the method proposed by Miettinen and Nurminen[20]; for AEs of symptomatic hypoglycaemia, urinary tract infection, genital infection, hypovolaemia, and polyuria/pollakiuria, between-group comparison point estimates, 95% CIs and P values were calculated. Descriptive statistics were calculated for all other safety endpoints.

With a randomized population of 69 patients per arm, the study was estimated to have a power of 90% to detect a true treatment difference of 0.5% in change from baseline in HbA1c at Week 24, assuming a true standard deviation (SD) of 0.85% (α = 0.05, two-sided) and a discontinuation rate of 10%.

## 3 | RESULTS

### 3.1 | Patient disposition and characteristics

A total of 173 patients were screened and 141 were randomized (70 to sitagliptin 50 mg once daily and 71 to placebo added to ipragliflozin 50 mg once daily). The primary reasons for not enrolling screened patients were not meeting inclusion criteria or meeting exclusion criteria (n = 30). Of patients randomized, 68 (97.1%) and 69 patients (97.2%) in the sitagliptin and placebo groups, respectively, completed the study medication (Figure 1). In the sitagliptin group, two patients discontinued study medication due to AEs and in the placebo group one discontinued due to an AE and one due to physician decision. The mean rate of compliance with study medication was 99.4% in the sitagliptin group and 99.6% in the placebo group.
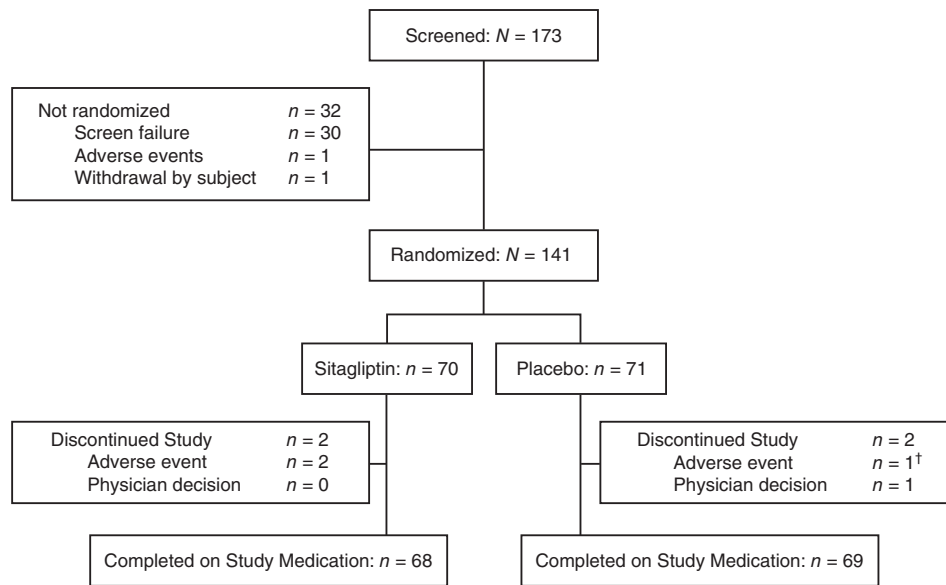
**FIGURE 1** Patient disposition. [†]This adverse event (AE) is not included in the summary AE table because it started during the placebo run-in period

Baseline demographics and efficacy variables were generally balanced between treatment groups (Table 1). The mean age was 55.5 ± 10.7 years, approximately 70% of patients were men, the mean baseline HbA1c was 8.0% ± 0.8, FPG was 150.0 mg/dL ± 26.1, 2-hour PMG was 213.6 mg/dL ± 48.3, body weight was 73.0 kg ± 13.8, and body mass index was 26.9 kg/m$^2$ ± 4.5. The mean duration of T2D was 9.2 ± 5.0 years.

## 3.2 | Efficacy

After 24 weeks of treatment, the least squares (LS) mean changes in HbA1c were −0.69% (95% CI −0.85, −0.53) with sitagliptin and 0.14% (95% CI −0.02, 0.29) with placebo (Table 2). The between-group difference was −0.83% (95% CI −1.05, −0.62; P <0.001 [Table 2]). HbA1c was decreased in the sitagliptin treatment group by Week 4 (the first measurement) and continued to diverge from the placebo group up to Week 24, the study primary timepoint (Figure 2). Across all subgroup categories, HbA1c reductions were greater with sitagliptin relative to placebo (Supplemental Table S1). Larger placebo-adjusted reductions in HbA1c were observed in those with higher baseline HbA1c (ie ≥median or ≥8.0%).

At Week 24, the between-group differences for change in 2-hour PMG, total PMG AUC$_{0-2h}$, and FPG, were −42.5 mg/dL (95% CI −53.7, −31.2), −67.0 mg·h/dL (95% CI −84.0, −50.0), and −11.2 mg/dL (95% CI −17.2, −5.2), respectively (P <0.001 for all the comparisons; Table 2).

The proportion of patients at HbA1c goal of <7.0% at Week 24 was greater in the sitagliptin group (30.0%, 21/70) compared with the placebo group (2.8%, 2/71). The adjusted odds ratio (95% CI), which is a measure of the likelihood of being at glycaemic goal of <7.0% with sitagliptin compared to placebo, was 15.1 (95% CI 3.4, 67.9; P <0.001).

**TABLE 1** Baseline demographic, anthropometric and disease characteristics of treatment groups

|  | Sitagliptin N = 70 | Placebo N = 71 |
|---|---|---|
| Age, years | 57.0 ± 11.6 | 54.0 ± 9.5 |
| Men, n (%) | 54 (77.1) | 45 (63.4) |
| Body weight, kg | 73.4 ± 14.4 | 72.6 ± 13.3 |
| Body mass index, kg/m$^2$ | 26.8 ± 4.4 | 27.1 ± 4.6 |
| HbA1c, % | 8.0 ± 0.8 | 8.1 ± 0.8 |
| FPG, mg/dL | 148.8 ± 25.4 | 151.2 ± 27.0 |
| 2-hour PMG, mg/dL | 211.9 ± 49.8 | 215.3 ± 47.0 |
| Total PMG AUC$_{0-2h}$, mg·h/dL | 414.4 ± 73.8 | 422.5 ± 68.2 |
| Insulin, microIU/mL | 7.4 ± 6.7 | 6.5 ± 4.4 |
| eGFR, mL/min/1.73 m$^2$ | 89.7 ± 16.4 | 93.9 ± 18.1 |
| Duration of T2D, years | 10.0 ± 5.4 | 8.3 ± 4.5 |
| Prior use of other OHAs, n (%) | | |
| Yes | 24 (34.3) | 25 (35.2) |

*Note:* Values are n (%) or mean ± standard deviation.
Abbreviations: AUC$_{0-2h}$, 0- to 2-hour area under the curve; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; OHA, oral hypoglycaemic agent; PMG, post-meal glucose; T2D, type 2 diabetes.

## 3.3 | Safety and tolerability

There were no notable differences between the treatment groups in the incidences of AEs, including those assessed by the investigator as drug-related (the 95% CI for all between-group differences in AE summary measures included 0, Table 3). Three patients in the sitagliptin group each had a serious AE (enteritis, gastric cancer, and suicide attempt). There were no serious drug-related AEs reported. The two

**TABLE 2** Primary and secondary efficacy endpoints at week 24

| Parameter | Sitagliptin (N = 70) | Placebo (N = 71) |
|---|---|---|
| HbA1c, % | | |
| Baseline | 8.0 ± 0.8 | 8.1 ± 0.8 |
| Week 24 | 7.3 ± 0.7 | 8.1 ± 0.9 |
| Change from baseline[a] | −0.69 (−0.85, −0.53) | 0.14 (−0.02, 0.29) |
| Change vs placebo[b] | −0.83 (−1.05, −0.62)* | — |
| 2-hour PMG[c], mg/dL | | |
| Baseline | 211.9 ± 49.8 | 215.3 ± 47.0 |
| Week 24 | 173.4 ± 34.3 | 215.5 ± 43.5 |
| Change from baseline[a] | −39.0 (−48.1, −29.9) | 3.4 (−5.5, 12.3) |
| Change vs placebo[b] | −42.5 (−53.7, −31.2)* | — |
| Total PMG AUC$_{0-2h}$[c], mg·h/dL | | |
| Baseline | 414.4 ± 73.8 | 422.5 ± 68.2 |
| Week 24 | 349.9 ± 50.2 | 418.4 ± 68.0 |
| Change from baseline[a] | −65.7 (−79.2, −52.2) | 1.3 (−11.9, 14.5) |
| Change vs placebo[b] | −67.0 (−84.0, −50.0)* | — |
| FPG[c], mg/dL | | |
| Baseline | 148.8 ± 25.4 | 151.2 ± 27.0 |
| Week 24 | 136.4 ± 23.9 | 149.0 ± 25.7 |
| Change from baseline[a] | −11.8 (−16.3, −7.4) | −0.6 (−5.0, 3.8) |
| Change vs placebo[b] | −11.2 (−17.2, −5.2)* | — |

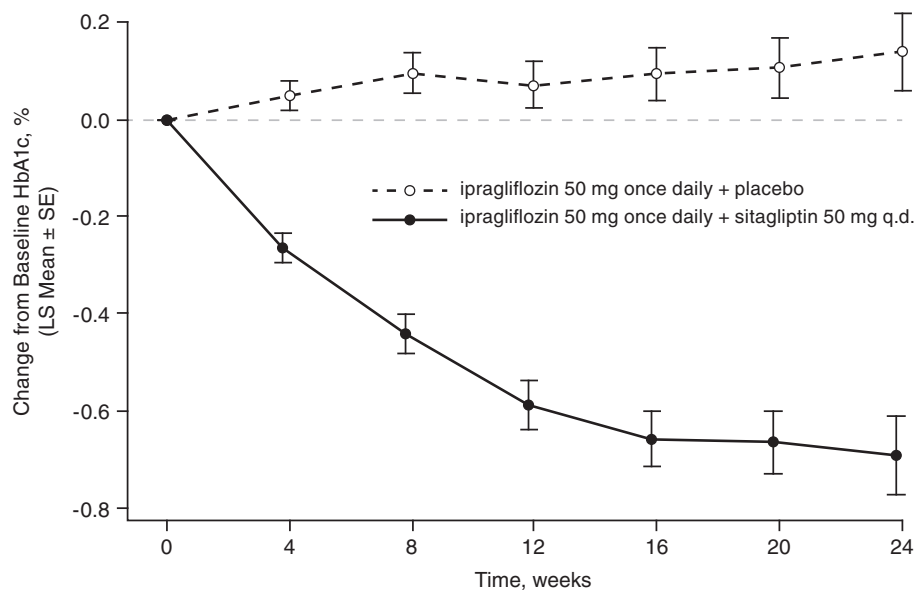*Note:* Values are mean ± standard deviation unless otherwise noted.

Abbreviations: AUC$_{0-2h}$, 0- to 2-hour post-meal glucose area under the curve; FPG, fasting plasma glucose; PMG, post-meal glucose.

[a]Least squares (LS) mean (95% CI).

[b]Difference in LS means (95% CI).

[c]To convert to mmol/L divide mg/dL value by 18.

*$P$ <0.001.



**FIGURE 2** Time course of glycated haemoglobin (HbA1c) change from baseline

AEs resulting in discontinuation of study medication in the sitagliptin group (melaena and the previously noted suicide attempt) were not assessed to be related to study medication. There were no deaths reported in either treatment group. The incidences of symptomatic hypoglycaemia were 0.0% in the sitagliptin add-on group and 1.4% in the placebo group; there were no severe hypoglycaemia events in

**TABLE 3** Adverse events (AEs) summary, prespecified AEs of interest, and specific AEs with incidence ≥4 in at least one treatment group

| Patients, n (%) | Sitagliptin N = 70 | Placebo N = 71 | Difference[a] |
|---|---|---|---|
| With one or more | | | |
| AEs | 38 (54.3) | 45 (63.4) | −9.1 (−24.9, 7.2) |
| Drug-related[b] AEs | 1 (1.4) | 5 (7.0) | −5.6 (−14.3, 1.4) |
| Serious AEs | 3 (4.3) | 0 (0.0) | 4.3 (−1.0, 11.9) |
| Serious drug-related[b] AEs | 0 (0.0) | 0 (0.0) | 0.0 (−5.2, 5.2) |
| Who died | 0 (0.0) | 0 (0.0) | — |
| Who discontinued study medication due to | | | |
| an AE | 2 (2.9) | 0 (0.0) | 2.9 (−2.4, 9.9) |
| a drug-related[b] AE | 0 (0.0) | 0 (0.0) | — |
| a serious AE | 1 (1.4) | 0 (0.0) | — |
| a serious drug-related[b] AE | 0 (0.0) | 0 (0.0) | — |
| With one or more AEs of | | | |
| symptomatic hypoglycaemia[c] | 0 (0.0) | 1 (1.4) | −1.4 (−7.6, 3.9) |
| severe hypoglycaemia[d] | 0 (0.0) | 0 (0.0) | — |
| asymptomatic hypoglycaemia[e] | 0 (0.0) | 1 (1.4) | — |
| With one or more AEs of | | | |
| urinary tract infection | 0 (0.0) | 2 (2.8) | −2.8 (−9.7, 2.5) |
| genital infection | 0 (0.0) | 1 (1.4) | −1.4 (−7.6, 3.9) |
| hypovolaemia | 1 (1.4) | 2 (2.8) | −1.4 (−8.5, 5.2) |
| polyuria/pollakiuria | 0 (0.0) | 1 (1.4) | −1.4 (−7.6, 3.9) |
| With specific AEs with incidence ≥4 in ≥1 treatment group | | | |
| Nasopharyngitis | 6 (8.6) | 18 (25.4) | −16.8 (−29.3, −4.6) |
| Eczema | 4 (5.7) | 0 (0.0) | 5.7 (0.4, 13.8) |

[a]Difference in % vs placebo; P values were calculated for between-group differences in AEs of symptomatic hypoglycaemia, urinary tract infection, genital infection, hypovolaemia, polyuria/pollakiuria; all were nonsignificant.
[b]Assessed by the investigator as related to study drug.
[c]Symptomatic hypoglycaemia: event with clinical symptoms reported by the investigator as hypoglycaemia (biochemical documentation not required).
[d]Severe episode: episode that required assistance, either medical or non-medical. Episodes with a markedly depressed level of consciousness, a loss of consciousness, or seizure are classified as having required medical assistance, whether or not medical assistance was obtained.
[e]Asymptomatic hypoglycaemia: event without symptoms attributed to hypoglycaemia, but with a glucose level ≤70 mg/dL.

either group (Table 3). The incidences of urinary tract infection, genital infection and polyuria/pollakiuria were all 0.0% in the sitagliptin group and 2.8%, 1.4% and 1.4%, respectively, in the placebo group (Table 3). The incidences of hypovolaemia were 1.4% and 2.8% in the sitagliptin and placebo groups, respectively (Table 3). The only specific AEs with incidence ≥4 in at least one treatment group were nasopharyngitis (6/70 [8.6%] in the sitagliptin group and 18/71 [25.4%] in the placebo group, between-group difference −16.8 [95% CI −29.3, −4.6]) and eczema (4/70 [5.7%] in the sitagliptin group and 0/71 [0.0%] in the placebo group, between-group difference 5.7% [95% CI 0.4, 13.8]) (Table 3). All reported events of eczema, including one event assessed as drug-related, were mild in intensity and resolved without discontinuation of study medication. There were no clinically meaningful findings related to laboratory safety measures or vital signs in either treatment group. However, there was a greater incidence of increased urea nitrogen (increase ≥50% and greater than the upper limit of normal at the last observed value during the treatment period) in the sitagliptin group (4/70 [5.7%]) compared to the placebo group (0/71

[0.0%]): between-group difference 5.7% (95% CI 0.4, 13.8). None of the patients with increased urea nitrogen reported dehydration or AEs related to renal function.

There was little change in mean ± SD body weight in either group (sitagliptin −0.0 kg ± 2.0; placebo −0.6 kg ± 1.8). There were no clinically meaningful changes in laboratory safety measures, ECG parameters, or vital signs including pulse rate and blood pressure. There were no reports of pancreatitis in either treatment group.

## 4 | DISCUSSION

In the present randomized, placebo-controlled, parallel-group, multi-centre, double-blind trial in Japanese patients with T2D and inadequate glycaemic control on ipragliflozin 50 mg once daily monotherapy, the addition of sitagliptin 50 mg once daily over 24 weeks provided a greater reduction in HbA1c by Week 24, compared to placebo. In addition, sitagliptin provided a greater reduction

in 2-hour PMG, PMG total AUC$_{0-2h}$, and FPG. The therapeutic efficacy of sitagliptin addition to ipragliflozin was confirmed by the observation that the proportion achieving an HbA1c level <7.0% was approximately 10-fold greater in the sitagliptin add-on group compared to the placebo group.

The reduction in HbA1c observed in the present study is similar to that observed in previous studies of sitagliptin added to existing OHA monotherapy in Japanese patients with T2D.[21-25] The result is also generally consistent with results of other studies with similar design in which a DPP-4 inhibitor was added on to an SGLT2 inhibitor in Japanese patients.[26,27] There are reports suggesting that the addition of a DPP-4 inhibitor to an SGLT2 inhibitor provides limited improvement in glycaemic control.[28-32] Abdul-Ghani[33] suggests that this results from the inability of DPP-4 inhibitors to overcome stimulation of endogenous glucose production by SGLT2 inhibitors. However, the robust efficacy of sitagliptin reported here and observed in other studies with similar design suggests that observations of more limited DPP-4 inhibitor efficacy in combination with SGLT2 inhibitors may not be mechanism-based, but may be related to differences in study design (eg, baseline glycaemic control, add-on vs co-initiation paradigm, initiation of SGLT2 inhibitor during the screening period or not) or to the population studied (ie, Japanese patients). Further, a recently completed companion study of similar design, in which ipragliflozin was added to background sitagliptin, showed similar efficacy in the ipragliflozin add-on group to that reported for the sitagliptin add-on group reported here.[34]

The addition of sitagliptin to ipragliflozin was generally well tolerated, with an AE profile consistent with the safety profiles of sitagliptin[7] and ipragliflozin.[35] No additional safety concerns were apparent in this study. Consistent with previous findings,[36] no weight gain was observed when sitagliptin was added-on to ipragliflozin. The incidences of AEs or drug-related AEs in the sitagliptin group were not clinically significant, compared with the placebo group. The addition of sitagliptin did not increase the incidences of any prespecified AEs (symptomatic hypoglycaemia, urinary tract infection, genital infection, hypovolaemia and polyuria/pollakiuria). Although the incidence of the specific AE of eczema was higher in the sitagliptin group compared with the placebo group, all events of eczema were mild in intensity and resolved without discontinuation of study medication. The incidence of drug-related AEs was low in both groups. There were no clinically meaningful findings in other safety variables including laboratory safety measures, vital signs and ECG parameters.

This study had several limitations. First, only Japanese patients were enrolled, so the findings may not be extrapolated to other ethnic groups, particularly considering the differences in pathophysiology of T2D between East Asian and White patients. Second, the study was of limited duration with a relatively small sample size. A longer and larger study would be required to better measure the durability of treatment efficacy, as well as to provide further understanding of the safety profile in this population, particularly with regard to uncommon events. Finally, the treatment was provided as co-administration of sitagliptin and ipragliflozin rather than as a fixed-dose combination.

In conclusion, the present study has demonstrated that in Japanese patients with T2D inadequately controlled with ipragliflozin monotherapy, the addition of sitagliptin provided significant improvement in glycaemic control and was generally well tolerated.

## CONFLICT OF INTEREST

YS has received contracted/collaborative research funds from Bayer, Boehringer Ingelheim and Terumo, scholarship grants from Arklay, Novo Nordisk, Ono, Sumitomo Dainippon and Taisho Toyama, and fees for consulting and/or lectures from Becton Dickinson, Boehringer Ingelheim, Kao, MSD, Novo Nordisk, Taisho, Taisho Toyama and Takeda. KK has received scholarship grants from Boehringer Ingelheim, Daiichi Sankyo and Mitsubishi Tanabe, and fees for consulting and/or lectures from Astellas, AstraZeneca, Boehringer Ingelheim, Fujifilm, Kissei, Kowa, Mitsubishi Tanabe, MSD, Novartis, Novo Nordisk, Sanofi, Sanwa Kagaku, Sumitomo Dainippon, Taisho Toyama and Takeda. TK has received contract research funds from AstraZeneca and Takeda, joint research funds from Daiichi Sankyo, grants from Astellas, Daiichi Sankyo, Eli Lilly, Kissei, Mitsubishi Tanabe, MSD, Novo Nordisk, Ono, Sanofi, Sumitomo Dainippon, Taisho and Takeda, fees for consulting and/or lectures from Abbott, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Cosmic, Daiichi Sankyo, Eli Lilly, Fujifilm, Johnson & Johnson, Kissei, Kowa, Kyowa Hakko Kirin, Medical Review, Medical View, Medscape Education, Medtronic Sofamor Danek, Mitsubishi Tanabe, MSD, Musashino Foods, Nipro, Novartis, Novo Nordisk, Ono, Sanofi, Sanwa Kagaku, Sumitomo Dainippon, Taisho, Takeda and Terumo, and has been in endowed chair from Asahi Mutual Life Insurance, Boehringer Ingelheim, Kowa, Mitsubishi Tanabe, MSD, Novo Nordisk, Ono and Takeda. TO, AS, MS, EAON, SSE, and KDK are current employees of MSD K.K. or Merck Sharp & Dohme Corp., subsidiaries of Merck & Co., Inc., Kenilworth, New Jersey, and may own stock/stock options in Merck & Co., Inc., Kenilworth, New Jersey. No other potential conflicts of interest relevant to this article are reported.

## AUTHOR CONTRIBUTIONS

YS, KK and TK contributed to finalization of the study protocol with provision of substantive suggestions for the study design, interpreted the results, and critically reviewed and/or revised the manuscript for important intellectual content. TO and AS conceived, designed and planned the study, interpreted the results, wrote sections of the initial draft, and critically reviewed and/or revised the manuscript for important intellectual content. SSE conceived, designed and planned the study, interpreted the results, and critically reviewed and/or revised the manuscript for important intellectual content. KDK interpreted the results, and critically reviewed and/or revised the manuscript for

important intellectual content. MS conceived, designed and planned the study, analysed the data, interpreted the results, and critically reviewed the manuscript for important intellectual content. EAON interpreted the results, wrote sections of the initial draft, and critically reviewed and/or revised the manuscript for important intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.