Received: 19 January 2021 | Revised: 12 May 2021 | Accepted: 23 May 2021

DOI: 10.1111/dom.14448

ORIGINAL ARTICLE

WILEY

Efficacy and safety of ipragliflozin in Japanese patients with type 2 diabetes and inadequate glycaemic control on sitagliptin

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Funding information
The study was funded and conducted by MSD K.K., Tokyo, Japan, as a joint development programme with Astellas Pharma Inc.

Abstract

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

Materials and Methods: The results of two clinical trials are reported. In both trials, patients had glycated haemoglobin (HbA1c) levels of 7.0% to 10.0% on sitagliptin 50 mg once daily 2 weeks prior to addition of ipragliflozin or placebo. In one trial (Trial 843), patients were randomized 1:1 to addition of blinded ipragliflozin 50 mg once daily (n = 73) or placebo (n = 70) for 24 weeks; the primary endpoint was efficacy (change in HbA1c at Week 24). In the other trial (Trial 849), open-label ipragliflozin 50 mg once daily was added for 52 weeks (n = 77); the primary objective was to assess safety/tolerability.

Results: In Trial 843, baseline characteristics were similar between groups (mean age 60.5 years, HbA1c 8.0%); after 24 weeks, adding ipragliflozin provided significantly greater reduction in HbA1c compared to placebo: least squares mean difference −0.77% (95% confidence interval −0.98, −0.57; P <0.001). In Trial 843, the incidences of adverse events (AEs) overall and prespecified AEs of clinical interest (symptomatic hypoglycaemia, urinary tract infection, genital infection, hypovolaemia, and polyuria/pollakiuria) were similar between groups. In Trial 849, specific AEs with incidence ≥5% were nasopharyngitis, pollakiuria, back pain, thirst, constipation, influenza and arthralgia; drug-related AEs reported in ≥2 patients were pollakiuria, thirst and constipation.

Conclusions: Ipragliflozin 50 mg once daily added on to sitagliptin 50 mg once daily monotherapy provided significant improvement in glycaemic control and was generally well tolerated in Japanese patients with T2D. ClinicalTrials.gov: NCT02577003, NCT02564211.

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

1 | INTRODUCTION

Treatment guidelines for type 2 diabetes (T2D)[1,2] recommend initiation of pharmacotherapy with a single oral hypoglycaemic agent (OHA) when diet and exercise do not sufficiently reduce blood glucose levels. In addition, the guidelines recognize that most patients will require an additional therapy with a complementary mechanism of action to achieve or maintain glycaemic control. Metformin is recommended by international guidelines as the initial OHA, with selection of a second medication based on an individual patient's clinical needs.[1] The Japanese guideline recommends that the initial pharmacological treatment be selected based on individual patient clinical condition and pathophysiology, and that an agent with a complementary mechanism of action be selected for coadministration therapy.[2]

Dipeptidyl peptidase-4 (DPP-4) inhibitors promote insulin secretion in a blood glucose-dependent manner by increasing active glucagon-like peptide-1 and glucose-dependent insulinotropic peptide levels, thereby decreasing glucose levels without an increased risk of hypoglycaemia.[3] Sitagliptin, a DPP-4 inhibitor, has been widely used for over 10 years and has a well-characterized safety profile.[4] In addition, the TECOS study demonstrated that addition of sitagliptin to usual care for T2D did not increase the risk of major adverse cardiovascular events.[5]

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a relatively new class of OHA. These drugs inhibit the renal reabsorption of glucose, thereby increasing glycosuria, leading to a reduction in blood glucose independent of insulin action.[6,7] Thus, improvement of glycaemic control with SGLT2 inhibitors is not associated with an increased risk of hypoglycaemia. Additionally, SGLT2 inhibitors have the benefit of promoting weight loss, primarily mediated by energy loss resulting from glycosuria.[7] Data from randomized, placebo-controlled clinical trials[8-13] demonstrate that the SGLT2 inhibitor ipragliflozin effectively reduces glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), and body weight in Japanese patients with T2D, while being generally safe and well tolerated.

Given the distinct mechanisms of action described above, it was considered likely that the combination of sitagliptin and ipragliflozin would provide additive glucose lowering. In addition, because of the limited increase in circulating insulin expected to be associated with the combination of these drugs, this combination was also considered unlikely to increase the risk of hypoglycaemia or weight gain, which are adverse effects associated with some other categories of OHA. Therefore, two phase III clinical trials were conducted to assess the efficacy and safety of adding ipragliflozin 50 mg once daily to treatment of Japanese patients with T2D and inadequate glycaemic control on sitagliptin 50 mg once daily monotherapy, as part of a programme to develop a fixed-dose combination of sitagliptin/ipragliflozin. One trial (Trial 843) was primarily designed to evaluate efficacy, while the other (Trial 849) was primarily concerned with safety. The results of both trials are reported here. The doses of sitagliptin and ipragliflozin used in both trials are the approved and most commonly used in Japan.

2 | METHODS

2.1 | Study designs

Trial 843 was randomized, placebo-controlled and double-blind (Supplemental Figure S2A). Trial 849 was non-controlled and open-label (Supplemental Figure S2B). Both were multicentre trials conducted in Japan, including a screening period of up to 2 weeks (for both Groups A and B, described below) and medication stabilization periods of 8 weeks (Trial 843) or 10 weeks (Trial 849) for patients requiring discontinuation of OHAs (Group A); Trial 843 had a 2-week placebo run-in period for all patients and a 24-week treatment period; Trial 849 had a 52-week treatment period. For Trial 843, after the placebo run-in, eligible patients were randomized centrally, using an internet-based, interactive response system, in a 1:1 ratio to receive either ipragliflozin 50 mg once daily or matching placebo. Randomization was stratified by prior use of OHAs other than sitagliptin 50 mg. Treatment with sitagliptin 50 mg once daily was continued throughout the study. For Trial 849, the 52-week treatment period began when eligible patients added ipragliflozin 50 mg once daily to previously initiated sitagliptin 50 mg once daily; both treatments were continued throughout the study. During Trial 849, patients exceeding prespecified glycaemic thresholds after Week 0 (confirmed central laboratory value of FPG >240 mg/dL up to Week 24 and FPG >200 mg/dL after Week 24) were to be rescued with open-label glimepiride. Throughout both studies, patients were encouraged to adhere to the diet/exercise regimen they were using prior to study entry. In addition, patients were not allowed to change medication for comorbidities (eg, hypertension, dyslipidaemia), unless clinically required.

During Trial 843, meal tolerance tests (MTTs) were carried out at Weeks 0 and 24, starting 30 minutes after administration of study treatment. The MTTs were performed under fasting conditions ≥10 hours. At Week 0, all patients received sitagliptin and placebo before the MTT; at Week 24, each received sitagliptin and either placebo or ipragliflozin. Blood samples for glucose assessment 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).

Trials 843 (ClinicalTrials.gov: NCT02577003) and 849 (ClinicalTrials.gov: NCT02564211) were conducted at 25 and 12 trial centres (Supplemental Appendix) in Japan between November 2015 and November 2016, and between October 2015 and March 2017, respectively, in accordance with the principles of Good Clinical Practice and were approved by the appropriate institutional review boards and regulatory agencies. Written informed consent was obtained from all study patients.

2.2 | Study populations

For both trials, at screening, eligible patients were male or female, aged ≥20 years, with T2D being treated with diet and exercise

therapy and meeting either of the following additional criteria: on a stable dose of sitagliptin 50 mg once daily and any single additional OHA or low-dose dual combination therapy prior to screening, with HbA1c ≥6.5% and ≤9.0% (Group A, which expands the sitagliptin monotherapy population after discontinuation of the additional OHA [s] and the subsequent medication stabilization period); or on a stable dose of sitagliptin 50 mg once daily and not on any additional OHAs prior to screening, with HbA1c ≥7.0% and ≤10.0%, and, for Trial 849, FPG ≤230 mg/dL (Group B). Prior to randomization (Trial 843) or enrolment (Trial 849), eligible patients met the following criteria: at Week −2, HbA1c ≥7.0% and ≤10.0% and FPG ≤230 mg/dL; at Week 0, on diet and exercise therapy for ≥8 weeks, OHAs except for sitagliptin discontinued ≥10 weeks, and on a stable dose of sitagliptin 50 mg once daily for ≥12 weeks.

Patients were excluded from the trials if they had type 1 diabetes or a history of ketoacidosis, unstable diabetic retinopathy, poorly controlled hypertension (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg), significant cardiovascular disease, active liver disease, renal disease or urological disorders, a history of malignancy or haematological disorders; if they had been treated with insulin or thiazolidinediones within 12 weeks prior to screening or with SGLT2 inhibitors at any time; or if they required treatment with systemic steroids. Laboratory exclusion criteria included serum alanine aminotransferase or aspartate aminotransferase levels >2 times the upper limit of normal, C-peptide levels <0.6 ng/mL, estimated glomerular filtration rate (eGFR) <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

For the placebo-controlled trial, Trial 843, the primary objectives were to assess the efficacy, safety and tolerability of the addition of ipragliflozin 50 mg once daily compared with placebo in Japanese patients with inadequate glycaemic control on sitagliptin 50 mg once daily monotherapy. The primary hypothesis was that addition of treatment with ipragliflozin 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 ipragliflozin with placebo on changes in FPG, 2-hour post-meal glucose (PMG), total PMG 2-hour area under the curve ($AUC_{0\text{-}2h}$), and body weight at Week 24. A tertiary objective was to compare the proportion of patients with HbA1c <7.0% at Week 24.

For the non-controlled open-label long-term trial, Trial 849, the primary objectives were to assess the safety and tolerability of the addition of ipragliflozin 50 mg once daily to sitagliptin 50 mg once daily monotherapy over 52 weeks. The secondary objective was to describe the effect of the addition of ipragliflozin 50 mg once daily on the change in HbA1c over 52 weeks. Other objectives were to describe the effect on change in FPG, body weight, and the proportion of patients with HbA1c <7.0% over 52 weeks.

2.4 | Safety evaluations

Safety assessment in both trials 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) and ECG. eGFR was calculated using the Japanese Equation 4 ($eGFR = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ [$\times 0.739$, if female]).[14] Symptomatic hypoglycaemia, urinary tract infection, genital infection, hypovolaemia, and polyuria/pollakiuria were identified as AEs of special interest in Trial 843 for comparison between ipragliflozin and placebo.

2.5 | Statistical analyses

The population for efficacy analyses included all randomized patients who received at least one dose of study treatment and who had at least one measurement (baseline or post-baseline) of the respective endpoint. Safety analyses included all patients who received ≥1 dose of treatment-period study medication. All statistical tests were conducted at $\alpha = 0.05$, two-sided.

In Trial 843, a longitudinal data analysis model[15] was used for the analysis of change from baseline in HbA1c. The model included terms for treatment, time (categorical), prior use of OHA (other than sitagliptin), and the interactions of treatment by time, time by prior use of OHA and treatment by time by prior use of OHA, and baseline eGFR value as a covariate, 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 FPG, 2-hour PMG, total PMG $AUC_{0\text{-}2h}$, and body weight at Week 24. In Trial 849, changes from baseline in HbA1c and other efficacy measures at various time points were summarized by descriptive statistics and 95% confidence intervals (CIs).

In Trial 843, the raw percentage of patients at the HbA1c goal of <7.0% at Week 24 was summarized by treatment. In addition, a logistic regression model including terms for treatment and prior use of OHAs, and baseline eGFR as a covariate was used to estimate the adjusted log odds ratio of being at the goal, relative to placebo, with multiple imputations carried out to impute missing data based on the longitudinal data analysis model used for analysis of HbA1c. The log odds ratio estimates from the respective imputed datasets were combined using the asymptotic theory of Robins and Wang.[16] The log odds ratio was back transformed into odds ratio for final reporting.

In Trial 849, the number and percentage of patients achieving HbA1c <7.0% at various times during the study, and the corresponding 95% CI (based on the method of Clopper and Pearson[17]), were calculated. The denominator used was the number of patients included in the efficacy analysis population having an HbA1c measurement at respective timepoints. Missing values were not imputed.

In both trials, safety and tolerability were assessed based on AEs, laboratory tests, ECG, and vital signs during the treatment period and through 14 days after treatment ended. In Trial 843, for the AE summary, including any AE, any drug-related AE, any serious AE, any

TABLE 1 Baseline demographic, anthropometric and disease characteristics of trial patients

	Trial 843		Trial 849
	Ipragliflozin/Sitagliptin $N = 73$	Placebo/Sitagliptin $N = 70$	Ipragliflozin/Sitagliptin $N = 77$
Age, years	61.0 ± 9.1	60.0 ± 10.4	58.9 ± 10.5
Men, n (%)	54 (74.0)	53 (75.7)	50 (64.9)
Body weight, kg	69.8 ± 11.7	70.1 ± 11.1	69.4 ± 11.8
BMI, kg/m^2	25.7 ± 3.5	26.0 ± 3.1	25.9 ± 3.4
HbA1c, %	8.1 ± 0.8	8.0 ± 0.6	8.0 ± 0.7
FPG, mg/dL	158.0 ± 33.2	163.0 ± 26.2	157.6 ± 27.3
2-hour PMG, mg/dL	225.3 ± 59.9	231.5 ± 48.9	-
Total PMG $AUC_{0\text{-}2h}$, mg·hr/dL	429.4 ± 86.3	443.4 ± 67.0	-
Insulin, microIU/mL	7.6 ± 6.3	7.8 ± 5.5	8.2 ± 4.4
eGFR, mL/min/1.73 m^2	82.0 ± 13.5	83.4 ± 16.7	85.0 ± 13.9
eGFR ≥90 mL/min/1.73 m^2, n (%)	20 (27.4)	17 (24.3)	29 (37.7)
eGFR <90 mL/min/1.73 m^2, n (%)	53 (72.6)	53 (75.7)	48 (62.3)
Duration of type 2 diabetes, years	9.6 ± 6.8	9.0 ± 5.9	7.8 ± 5.1
Prior use of other OHAs, n (%)			
Yes	31 (42.5)	30 (42.9)	8 (10.4)
No	42 (57.5)	40 (57.1)	69 (89.6)
Systolic BP, mm Hg	131.7 ± 15.1	129.2 ± 14.4	129.2 ± 14.7
Diastolic BP, mm Hg	78.1 ± 8.8	78.1 ± 10.7	78.3 ± 10.0
HDL cholesterol, mg/dL	53.9 ± 14.1	53.5 ± 14.0	53.1 ± 11.6
LDL cholesterol, mg/dL	111.3 ± 25.4	109.9 ± 23.9	121.4 ± 31.3
Triglycerides, mg/dL	114.5 ± 58.5	140.8 ± 130.9	127.7 (92.6)

Note: Values are mean ± standard deviation unless otherwise noted.
Abbreviations: $AUC_{0\text{-}2h}$, 0–2 hour area under the curve; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OHA, oral hypoglycaemic agent; PMG, post-meal glucose.

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 in ≥4 patients in either treatment group, between-group comparison point estimates with 95% CIs were calculated using the method of Miettinen and Nurminen[18]; 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. In Trial 849, AEs and PDLCs were summarized by the number and percentage of patients who experienced respective events.

With a sample size of 69 patients per arm, Trial 843 was estimated to have 90% power 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% ($\alpha = 0.05$, two-sided) and a discontinuation rate of 10%.

In Trial 849, with a sample size of 75 patients, if the underlying incidence for an AE or a specific safety event of interest was 2%, then there was a 78% chance that it would be observed in at least one patient among the 75 enrolled. With 75 patients enrolled, the half-width of the 95% CI for change from baseline in HbA1c was 0.23% if the SD estimate was 1%.

3 | RESULTS

3.1 | Patient disposition and characteristics

In Trial 843, 179 patients were screened, and 143 were randomized (73 to the ipragliflozin 50 mg once daily group, and 70 to the placebo group). Of patients randomized, 71 (97.3%) and 65 (92.9%) in the ipragliflozin and placebo groups, respectively, completed the study on study medication (Supplemental Figure S1A). In the ipragliflozin group, two patients discontinued due to AEs and in the placebo group, four discontinued due to AEs and one due to withdrawal by patient.

In Trial 849, 92 patients were screened and 77 were enrolled. Treatment was completed by 73 patients (94.8%); four patients discontinued due to AEs (Supplemental Figure S1B). No patients required rescue medication.

In Trial 843, baseline demographics and efficacy variables were generally balanced between treatment groups (Table 1). In Trial 849, baseline characteristics were similar to those in Trial 843, except for the slightly shorter duration of diabetes and higher proportion of patients without prior use of other OHAs (Table 1).

TABLE 2 Trial 843: Primary and secondary efficacy endpoints at Week 24

	Trial 843	
Variable	**Ipragliflozin/Sitagliptin (*N* = 73)**	**Placebo/Sitagliptin (*N* = 70)**
HbA1c, %		
Baseline	8.1 ± 0.8	8.0 ± 0.6
Week 24	7.2 ± 0.5	7.9 ± 0.9
Change from baseline[a]	−0.84 (−0.99, −0.69)	−0.07 (−0.22, 0.09)
Change vs. placebo[b]	−0.77 (−0.98, −0.57)*	-
FPG[c], mg/dL		
Baseline	158.0 ± 33.2	163.0 ± 26.2
Week 24	129.7 ± 16.6	157.2 ± 28.5
Change from baseline[a]	−30.3 (−35.5, −25.0)	−2.1 (−7.6, 3.3)
Change vs. placebo[b]	−28.1 (−34.8, −21.5)*	-
2-hour PMG[c], mg/dL		
Baseline	225.3 ± 59.9	231.5 ± 48.9
Week 24	175.6 ± 29.0	225.3 ± 48.1
Change from baseline[a]	−52.4 (−61.5, −43.2)	−3.8 (−13.3, 5.7)
Change vs. placebo[b]	−48.5 (−59.6, −37.5)*	-
Total PMG $AUC_{0\text{-}2h}$[c], mg·h/dL		
Baseline	429.4 ± 86.3	443.4 ± 67.0
Week 24	347.4 ± 44.3	435.8 ± 78.1
Change from baseline[a]	−86.9 (−101.0, −72.9)	−2.3 (−17.0, 12.3)
Change vs. placebo[b]	−84.6 (−102.6, −66.6)*	-
Body weight, kg		
Baseline	69.8 ± 11.7	70.1 ± 11.1
Week 24	67.4 ± 11.7	69.5 ± 10.9
Change from baseline[a]	−2.4 (−2.9, −1.9)	−0.6 (−1.1, −0.1)
Change vs. placebo[b]	−1.8 (−2.5, −1.1)*	-

Note: Values are mean ± standard deviation unless otherwise noted.
Abbreviations: $AUC_{0\text{-}2h}$, 0–2 hour area under the curve; FPG, fasting plasma glucose; LS, least squares; PMG, post-meal glucose.
[a]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.

3.2 | Efficacy

3.2.1 | Trial 843 (placebo-controlled)

After 24 weeks of treatment, the least squares (LS) mean changes in HbA1c were −0.84% (95% CI −0.99, −0.69) with ipragliflozin and −0.07% (95% CI −0.22, 0.09) with placebo (Table 2); the between-group difference was −0.77% (95% CI −0.98, −0.57; P <0.001 [Table 2]). HbA1c was decreased in the ipragliflozin group by Week 4, reached a near maximal reduction by Week 12, and continued to be maximally reduced up to Week 24 (Figure 1A).

At Week 24, the between-group differences in LS mean changes in FPG, 2-hour PMG, total PMG $AUC_{0\text{-}2h}$, and body weight were −28.1 mg/dL (95% CI −34.8, −21.5), −48.5 mg/dL (95% CI −59.6, −37.5), −84.6 mg·hr/dL (−102.6, −66.6), and − 1.8 kg (95% CI −2.5, −1.1), respectively (P <0.001 for all comparisons; Table 2).

The proportion of study patients at HbA1c goal of <7.0% at Week 24 was greater in the ipragliflozin group (31.5%, 23/73) compared with the placebo group (8.6%, 6/70). The adjusted odds ratio (95% CI), which is a measure of the likelihood of being at glycaemic goal of <7.0% with ipragliflozin treatment compared to placebo, was 6.2 (95% CI 2.2, 17.7; P <0.001).

3.2.2 | Trial 849 (non-controlled)

The mean change in HbA1c after 52 weeks of treatment with ipragliflozin added on to sitagliptin was −0.80% (95% CI −0.96,

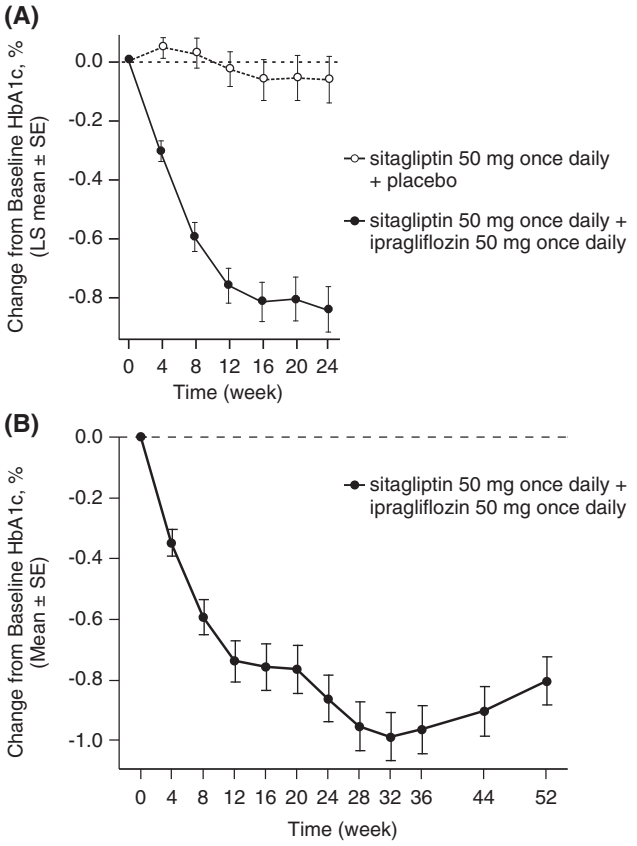

FIGURE 1 Time course of glycated haemoglobin (HbA1c) change from baseline; A, Trial 843, Weeks 0–24. B, Trial 849, Weeks 0–52. LS, least squares; SE, standard error

−0.65). Most HbA1c reduction was observed by Week 12 and the decrease was generally maintained up to 52 weeks of treatment (Figure 1B). At Week 52 the mean change in FPG was −24.5 mg/dL (95% CI −30.2, −18.8) and in body weight it was −2.3 kg (95% CI −2.9, −1.8). During the study, the proportion of patients at HbA1c of <7.0% ranged from 9.2% (Week 4) to 51.4% (Week 28). At Week 52, 29/73 patients had HbA1c <7.0% (proportion = 39.7% [95% CI 28.5, 51.9]). No patient required rescue medication.

3.3 | Safety and tolerability

3.3.1 | Trial 843 (placebo-controlled)

There were no notable between-group differences 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). No deaths were reported in the study. Two patients in the ipragliflozin add-on group reported a nonfatal serious AE (pulmonary mass and cerebral infarction) and four in the placebo group each reported one (cardiomyopathy, ureterolithiasis, angina pectoris, and sleep apnoea syndrome). The event of cerebral infarction was assessed by the investigator as related to study drug (ipragliflozin). Two patients in the ipragliflozin add-on group reported three AEs leading to discontinuation of study medication (cerebral infarction previously noted in one, pollakiuria and headache in another), and four in the placebo group each reported one (cardiomyopathy previously noted, blood glucose increased [two events], and cystitis). The three AEs leading to discontinuation, reported in two patients in the ipragliflozin add-on group, were assessed by the investigator as related to study drug (ipragliflozin). All events other than cerebral infarction resolved after discontinuation of study medication.

The incidences of hypoglycaemia (symptomatic or asymptomatic) and prespecified AEs of interest were low and similar in both groups (Table 3). There were no events of severe hypoglycaemia reported in either group. There were no clinically meaningful changes from baseline in laboratory safety measures, including eGFR (Supplemental Table S1), or in pulse rate and ECG variables. The addition of ipragliflozin to sitagliptin resulted in slight decrease in blood pressure (Supplemental Table S1).

3.3.2 | Trial 849 (non-controlled)

The incidences of overall AEs and drug-related AEs were 77.9% and 24.7% (Table 4). Specific AEs with incidence ≥5% were nasopharyngitis, pollakiuria, back pain, thirst, constipation, influenza, and arthralgia; among drug-related AEs, those reported in ≥2 patients were pollakiuria, thirst and constipation; the intensities of all were mild or moderate (Table 4). No AEs of hypoglycaemia were reported. Nonfatal serious AEs were angina pectoris (n = 2), contusion, papillary thyroid cancer, and breast cancer (n = 1 each); none was assessed as drug-related. Four AEs (pollakiuria, drug eruption, nocturia, and previously noted breast cancer) each led to a patient discontinuing from the study. Of these, pollakiuria, drug eruption, and nocturia were assessed by the investigator as study drug (ipragliflozin) related; each was of moderate intensity and the affected individuals recovered after discontinuation of study medication.

There were small increases in haemoglobin, haematocrit, red blood cell count, urea nitrogen, and some serum electrolytes. There was a small decrease in eGFR (Supplemental Table S1). None of these were considered clinically meaningful.

Although there were laboratory values that met PDLC for individual patients (including increased haemoglobin; increased or decreased white blood cell count, neutrophil count, or lymphocyte count; increased alkaline phosphatase, urea nitrogen, Na, or K; decreased Ca, or Mg), none was considered clinically significant and no related laboratory AEs were reported.

A slight reduction in blood pressure was observed after initiation of ipragliflozin treatment (Supplemental Table S1). No notable changes in pulse rate or in ECG variables were observed.

4 | DISCUSSION

In Trial 843, a randomized, placebo-controlled, parallel-group, multicentre double-blind trial in Japanese patients with T2D and

TABLE 3 Summary of Trial 843 adverse events, hypoglycaemia, and prespecified adverse events of interest

Patients, n (%)	Ipragliflozin/Sitagliptin (*N* = 73)	Placebo/Sitagliptin (*N* = 70)	Difference*
With one or more			
AEs	37 (50.7)	46 (65.7)	−15.0 (−30.5, 1.2)
Drug-related[a] AEs	8 (11.0)	4 (5.7)	5.2 (−4.4, 15.3)
Serious AEs	2 (2.7)	4 (5.7)	−3.0 (−11.5, 4.5)
Serious drug-related[a] AEs	1 (1.4)	0 (0.0)	1.4 (−3.9, 7.4)
Who died	0 (0.0)	0 (0.0)	-
Who discontinued study medication due to			
An AE	2 (2.7)	4 (5.7)	−3.0 (−11.5, 4.5)
A drug-related[a] AE	2 (2.7)	0 (0.0)	-
A serious AE	1 (1.4)	1 (1.4)	-
A serious drug-related[a] AE	1 (1.4)	0 (0.0)	-
With one or more AE of			
Symptomatic hypoglycaemia[b]	0 (0.0)	1 (1.4)	−1.4 (−7.7, 3.6)
Severe hypoglycaemia[c]	0 (0.0)	0 (0.0)	-
Asymptomatic hypoglycaemia[d]	0 (0.0)	1 (1.4)	-
With one or more AE of			
Urinary tract infection	1 (1.4)	1 (1.4)	−0.1 (−6.5, 6.1)
Genital Infection	0 (0.0)	0 (0.0)	0.0 (−5.2, 5.0)
Hypovolemia	3 (4.1)	2 (2.9)	1.3 (−6.3, 9.0)
Polyuria/pollakiuria	2 (2.7)	0 (0.0)	2.7 (−2.6, 9.5)

Abbreviation: AE, adverse event.

[a]Assessed by the investigator as related to study drug.

[b]Symptomatic hypoglycaemia: event with clinical symptoms reported by the investigator as hypoglycaemia (biochemical documentation not required).

[c]Severe hypoglycaemia: event that required assistance, either medical or nonmedical. Event with a markedly depressed level of consciousness, a loss of consciousness, or seizure was classified as having required medical assistance, whether or not medical assistance was obtained.

[d]Asymptomatic hypoglycaemia: event without symptoms attributed to hypoglycaemia, but with a glucose level ≤70 mg/dL.

*Difference in % vs placebo; *P* values were calculated for between-group differences in AEs of symptomatic hypoglycaemia, urinary tract infection, genital infection, hypovolemia, polyuria/pollakiuria; all were nonsignificant.

inadequate glycaemic control on sitagliptin 50 mg once daily monotherapy, the addition of ipragliflozin 50 mg once daily over 24 weeks was generally well tolerated and provided a greater improvement in glycaemic control and a reduction in body weight compared to placebo. There was no clinically meaningful difference in the incidence of AEs in the ipragliflozin add-on group compared with the placebo group.

In Trial 849, an open-label, long-term treatment trial in a population like that in Trial 843, addition of ipragliflozin 50 mg once daily over 52 weeks was generally well tolerated. Clinically meaningful improvement of glycaemic variables observed after initiation of ipragliflozin treatment was generally maintained to Week 52 without need of rescue medication. Meaningful reduction of body weight was also observed. An increase in HbA1c was observed after a nadir at Week 32. Similar effects are typically observed in trials of antihyperglycaemic agents and there are several possible explanations: first, decrease in glycaemic control can occur due to loss of a trial effect, when patients become familiar with trial activities and gradually return to behaviour that had changed as a result of trial participation; second, a gradual loss of glycaemic control due to disease progression may occur; finally, it is possible that these common effects were amplified in this trial by a seasonal effect on glycaemic control.[19] Enrolment for this study occurred during winter in Japan (the first and last patients' Week 0 visits were in November and the following March, respectively). Therefore, the middle of the treatment period occurred during summer when glycaemic control may be greatest, and finished as winter began, when glycaemic control can decrease again.

In both trials, the AE profile was consistent with the safety profiles of ipragliflozin[20] and sitagliptin.[4] No new safety concerns were apparent. No AEs of symptomatic or asymptomatic hypoglycaemia were reported in the ipragliflozin add-on group.

In Trial 849, most of the AEs assessed as drug-related by the investigator (events of pollakiuria and thirst) have previously been observed to be associated with use of SGLT2 inhibitors.[21] These events are likely to be mechanism related, caused by osmotic diuresis related to increased urine glucose excretion. It has been observed with another SGLT2 inhibitor that diuresis begins soon after initiation of treatment and is transient.[22] In the present study, 10 out of 11 events of pollakiuria and six out of eight events of thirst occurred before treatment-day 28, and most cases were reported as resolving

TABLE 4 Trial 849 adverse events and hypoglycaemia summary

Patients, n (%)	Ipragliflozin/ Sitagliptin $N = 77$
With one or more	
AEs	60 (77.9)
Drug-related[a] AEs	19 (24.7)
Serious AEs	5 (6.5)
Serious drug-related[a] AEs	0 (0.0)
Who died	0 (0.0)
Who discontinued study medication due to	
An AE	4 (5.2)
A drug-related[a] AE	3 (3.9)
A serious AE	1 (1.3)
A serious drug-related[a] AE	0 (0.0)
With one or more AEs of	
Symptomatic hypoglycaemia[b]	0 (0.0)
Asymptomatic hypoglycaemia[c]	0 (0.0)
With specific AEs occurring in ≥5% of patients	
Nasopharyngitis	22 (28.6)
Back pain	11 (14.3)
Pollakiuria	11 (14.3)
Thirst	8 (10.4)
Constipation	6 (7.8)
Influenza	5 (6.5)
Arthralgia	4 (5.2)
With specific drug-related AEs occurring in ≥2 patients	
Pollakiuria	11 (14.3)
Thirst	6 (7.8)
Constipation	4 (5.2)

Abbreviation: AE, adverse event.
[a]Assessed by the investigator as related to study drug.
[b]Symptomatic hypoglycaemia: event with clinical symptoms reported by the investigator as hypoglycaemia (biochemical documentation not required).
[c]Asymptomatic hypoglycaemia: event without symptoms attributed to hypoglycaemia, but with a glucose level ≤70 mg/dL.

or having resolved without discontinuation of study medication. Thus, the observations reported as related to ipragliflozin use are consistent with the profile of an SGLT2 inhibitor.

Postmarketing case reports have resulted in warnings of dehydration and the possible increased risks of embolism and cerebral infarction in the labels of SGLT2 inhibitors in Japan. However, recent large, randomized studies for cardiovascular risk assessment did not find increased risk of stroke associated with use of SGLT2 inhibitors.[23-25] In Trial 843, cerebral infarction was reported as a drug-related serious AE in a patient; the investigator reported no obvious signs of dehydration (eg, laboratory variable changes) in association with the serious AE, and the patient had multiple cardiovascular risk factors including advanced age, smoking history, coronary arterial stent insertion history, hypertension, angina pectoris and hyperlipidaemia. Carotid artery stenosis was concurrently reported as a nonserious drug-related event in the patient.

In both trials, the addition of ipragliflozin resulted in small decreases in blood pressure (both systolic and diastolic), which are known effects of SGLT2 inhibitors generally considered to contribute to the favourable benefit:risk profile of the SGLT2 drug class.[26] There were no clinically meaningful changes in laboratory safety measures, pulse rate or ECG variables.

The two studies had several limitations. First, only Japanese patients were enrolled, so the findings may not be extrapolatable to other ethnic groups, particularly considering the differences in pathophysiology of T2D between East Asian and White patients. Second, the treatment was provided as coadministration of sitagliptin and ipragliflozin rather than as a fixed-dose combination. Thus, it will be important to monitor the clinical benefits and risks associated with the fixed-dose combination that is already being used in clinical practice in Japan.

In conclusion, the present trials showed that in Japanese patients with T2D inadequately controlled on sitagliptin monotherapy, the addition of ipragliflozin provided significant improvement in glycaemic variables and body weight and was generally well tolerated.

ACKNOWLEDGMENTS

The authors thank Jennifer Rotonda PhD and Michele McColgan BA, of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey, for their assistance in preparing this paper for publication, and Kenichi Kazuta MS and Noriko Akiyama MS, of Astellas Pharma Inc., for their support in the study preparation.

CONFLICTS OF INTEREST

KK has received scholarship grants from Boehringer Ingelheim, Daiichi Sankyo, Taisho and Mitsubishi Tanabe; and fees for consulting and/or lectures from Astellas, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Fujifilm, Kowa, Mitsubishi Tanabe, MSD, Novo Nordisk Pharma, Ono, 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 an endowed chair for Asahi Mutual Life Insurance, Boehringer Ingelheim, Kowa, Mitsubishi Tanabe, MSD, Novo Nordisk, Ono and Takeda. 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 consulting and/or lectures fees from Becton

Dickinson, Boehringer Ingelheim, Kao, MSD, Novo Nordisk, Taisho, Taisho Toyama and Takeda. TO, AS, MS, EAON, SSE, and KDK are current employees of MSD K.K., Tokyo, Japan, or Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, New Jersey USA, and may own stock/stock options in Merck & Co., Inc., Kenilworth, NJ, USA. No other potential conflicts of interest relevant to this article are reported.

AUTHOR CONTRIBUTIONS

KK, TK and YS 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.

DATA AVAILABILITY STATEMENT

The data sharing policy, including restrictions, of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the Engage Zone site or via email to dataaccess@merck.com.

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SUPPORTING INFORMATION

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

How to cite this article: Kaku K, Kadowaki T, Seino Y, et al. Efficacy and safety of ipragliflozin in Japanese patients with type 2 diabetes and inadequate glycaemic control on sitagliptin. *Diabetes Obes Metab*. 2021;23(9):2099–2108. https://doi.org/10.1111/dom.14448