Diabetes Ther (2018) 9:1549–1567
https://doi.org/10.1007/s13300-018-0455-8

ORIGINAL RESEARCH

Ipragliflozin Add-on Therapy to a GLP-1 Receptor Agonist in Japanese Patients with Type 2 Diabetes (AGATE): A 52-Week Open-Label Study

Hisamitsu Ishihara · Susumu Yamaguchi · Ikko Nakao · Taishi Sakatani

Received: February 13, 2018 / Published online: June 20, 2018

ABSTRACT

Introduction: Few data are available regarding ipragliflozin treatment in combination with glucagon-like peptide-1 (GLP-1) receptor agonists. The aim of this study was to evaluate the efficacy and safety of ipragliflozin in combination with GLP-1 receptor agonists in Japanese patients with inadequately controlled type 2 diabetes mellitus (T2DM).

Methods: This multicenter study (consisting of three periods: a 4-week washout period, a 6-week observation period, and a 52-week open-label treatment period) included patients aged ≥ 20 years who received a stable dose/regimen of a GLP-1 receptor agonist either solely or in combination therapy with a sulfonylurea for ≥ 6 weeks, with glycosylated hemoglobin (HbA1c) of ≥ 7.5% and a fasting plasma glucose (FPG) of ≥ 126 mg/dL. Ipragliflozin treatment was given at a fixed dose of 50 mg/day for 20 weeks, followed by 50 or 100 mg/day for 32 weeks. Changes from baseline in glycemic control and other parameters were examined; safety was also assessed.

Results: The mean changes in HbA1c and body weight from baseline to end of treatment were − 0.92% and − 2.69 kg, respectively, in all ipragliflozin-treated patients (n = 103). Overall, sustained reductions from baseline were observed for HbA1c, FPG, self-monitored blood glucose, and body weight during the 52-week treatment. The dose increase of ipragliflozin to 100 mg/day resulted in better glycemic control and weight reduction for patients in whom the 50-mg dose was insufficient. Overall, 46.6% (48/103) of patients experienced drug-related adverse events. The most common drug-related treatment-emergent adverse events were pollakiuria (9.7%), hypoglycemia (8.7%), constipation (6.8%), and thirst (5.8%).

Conclusion: Combined therapy with ipragliflozin and GLP-1 receptor agonists/sulfonylureas was significantly efficacious in reducing glycemic parameters in patients with T2DM with inadequate glycemic control, and no major safety concerns were identified. The

Enhanced digital features To view enhanced digital features for this article go to https://doi.org/10.6084/m9.figshare.6395915.

AGATE: A long-term study to show efficacy and safety of ipragliflozin in Add-on therapy with GLP-1 receptor Agonists in Type 2 diabetEs mellitus patients.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13300-018-0455-8) contains supplementary material, which is available to authorized users.

H. Ishihara (✉)
Division of Diabetes and Metabolic Diseases, Nihon University School of Medicine, 30-1 Oyaguchikami-cho, Itabashi-ku, Tokyo 173-8610, Japan
e-mail: ishihara.hisamitsu@nihon-u.ac.jp

S. Yamaguchi · I. Nakao · T. Sakatani
Astellas Pharma Inc., 2-5-1 Nihonbashi-Honcho Chuo-ku, Tokyo 103-8411, Japan

results from this study suggest that ipragliflozin can be recommended as a well-tolerated and effective add-on therapy to a GLP-1 receptor agonist for the treatment of T2DM.
Trial registration: ClinicalTrials.gov (identifier: NCT02291874).
Funding: Astellas Pharma Inc., Tokyo, Japan.

Keywords: Diabetes mellitus, type 2; Glucagon-like peptide-1 receptor; Ipragliflozin; Sodium-glucose cotransporter 2

INTRODUCTION

As lifestyle and dietary practices are fundamental contributors to the obesity and type 2 diabetes epidemics worldwide [1, 2], lifestyle changes and exercise are key aspects of treatment. However, achieving adequate glycemic control solely through lifestyle changes is difficult in many cases; thus, single- or multiple-drug therapies are indicated for the treatment of type 2 diabetes mellitus (T2DM).

Currently available oral glucose-lowering agents include sulfonylureas (SUs), biguanides, thiazolidinediones, and α-glucosidase inhibitors [3]. However, it has been reported that despite receiving these drug therapies, only 37% of patients attain adequate blood glucose control [4], suggesting that there is an unmet need for agents that can effectively control blood glucose. Additionally, some of the existing glucose-lowering agents have several shortcomings, such as weight gain (thiazolidinediones, SUs, and insulin), hypoglycemia (SUs, glinides, and insulin), and gastrointestinal side effects (metformin and α-glucosidase inhibitors) [5].

Ipragliflozin is a novel sodium-glucose cotransporter 2 (SGLT2) selective inhibitor that inhibits SGLT2-mediated glucose reabsorption in the renal proximal tubules and facilitates glucose excretion in urine, thereby lowering blood glucose levels [6, 7]. During the drug development process, several randomized controlled trials demonstrated the efficacy and safety of ipragliflozin alone and in combination with other glucose-lowering agents [8–13]. Glucagon-like peptide-1 (GLP-1) receptor agonists are incretin-based, injectable antidiabetic agents that act directly on glucose-dependent pancreatic islet cell hormone secretion and improve fasting and postprandial blood glucose control without risk of hypoglycemia. GLP-1 receptor agonists also promote body weight loss through the stimulation of GLP-1 receptors in hypothalamic satiety centers [14]. GLP-1 receptor agonists are introduced when patients cannot achieve their goals for glycemic control by means of diet and exercise therapies and/or oral glucose-lowering agents [15].

The aim of this study was to evaluate the efficacy and safety of ipragliflozin treatment in combination with GLP-1 receptor agonists in Japanese patients with T2DM who did not achieve adequate glycemic control with GLP-1 receptor agonist therapy during a minimum period of 6 weeks prior to enrollment.

METHODS

Study Design

This multicenter (Electronic Supplementary Material 1) open-label study consisted of three periods: a 4-week washout period (only for patients using glucose-lowering agents other than GLP-1 receptor agonists and SUs), a 6-week observation period, and a 52-week open-label treatment period. During the observation period, we confirmed the stability of glycosylated hemoglobin (HbA1c). Following the observation period, patients were registered and began the open-label treatment period. The dose of the study drug was increased according to the dose-escalation criteria defined in this study. The 52-week open-label treatment period comprised an initial 20-week period of administration of ipragliflozin at a fixed dose of 50 mg/day. Patients with an HbA1c of $> 7.0\%$ at week 16 (considered to be poor responders to the 50-mg ipragliflozin dose) were eligible for a dose increase to 100 mg/day starting on week 20. In the following 32 weeks, patients received ipragliflozin at either 50 mg or 100 mg/day. The study design is shown in Fig. 1.

The study was conducted at 19 sites in Japan. All procedures performed in the study were in accordance with the ethical standards of the

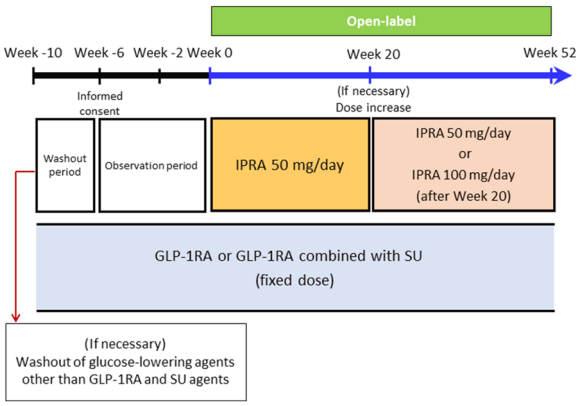

Fig. 1 Study design. *GLP-1RA* Glucagon-like peptide-1 receptor agonist, *IPRA* ipragliflozin, *SU* sulfonylurea

institutional review board of each site and with the 1964 Helsinki declaration and its later amendments. Additionally, the study complied with all relevant laws and regulations, including Good Clinical Practice and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines. Informed consent was obtained from all individual participants included in the study. This study was registered at ClinicalTrials.gov (identifier: NCT02291874).

Study Eligibility and Withdrawal

The inclusion criteria were as follows: age $\geq$ 20 years; diagnosis of type 2 diabetes $\geq$ 12 weeks before enrollment; prescription of a stable dose/regimen of a GLP-1 receptor agonist or concomitant prescription of a stable dose/regimen of a GLP-1 receptor agonist and SU for $\geq$ 6 weeks; HbA1c $\geq$ 7.5% and $\leq$ 10.5%, with a maximum change in HbA1c of $\pm$ 1% at visit 1 (week $-$ 6) and visit 2 (week $-$ 2); body mass index (BMI) of between 20.0 and 45.0 kg/m^2; and fasting plasma glucose (FPG) level of $\geq$ 126 mg/dL at visit 2 (week $-$ 2) for those receiving SU therapy.

The main exclusion criteria were as follows: diagnosis of type 1 diabetes mellitus; urinary symptoms (dysuria, anuria, oliguria, and urinary retention); history of recurrent urinary tract or genital infection; proliferative retinopathy; renal disease; history of pancreatitis or cerebrovascular or cardiovascular diseases; chronic disease(s) that required continuous use of non-topical corticosteroids or immunosuppressants; severe infections; malignant tumors; alcoholism or other addictions; unstable psychiatric disorder; women with child-bearing potential not using contraceptives appropriately; history of allergy to ipragliflozin and/or similar drugs; previous participation in a clinical study or postmarketing surveillance within 12 weeks of enrollment; and patients who were unable or unwilling to adhere to the study procedures.

Patients could be withdrawn at any time during the study for a number of reasons, including safety concerns and severe hypoglycemia (hypoglycemic coma, convulsions, or other conditions requiring infusion or injection of glucose or glucagon). Additionally, patients were withdrawn if their HbA1c was > 8.5% on two consecutive visits from week 24 onwards and if the FPG level exceeded 270 mg/dL on two consecutive measurements.

Treatments

Patients underwent liraglutide monotherapy or treatment with liraglutide or other GLP-1 receptor agonist in combination with an SU at a constant dose/dose regimen for at least 6 weeks before visit 1. Visit 1 (week $-$ 6) was then followed by the 6-week observation period, registration, and enrollment into the open-label treatment period. At the beginning of the 20-week open-label treatment period, all patients received 50 mg/day of ipragliflozin. At week 20, the ipragliflozin dose could be increased to 100 mg/day in patients whose HbA1c was $\geq$ 7.0% (poor responders) and for whom the investigators considered there were no safety concerns. Treatment was discontinued in patients whose HbA1c was > 8.5% at two consecutive visits from visit 10 (week 24) onwards. From the observation period to the end of the treatment period, the type or dose/dose regimen of GLP-1 receptor agonists and SU could not be changed. Once the dose of ipragliflozin was escalated, the patient continued to

receive ipragliflozin at the escalated dose (100 mg/day), in principle, until the end of the treatment period. However, if safety concerns were raised after the dose increase, the dose could be reduced to 50 mg/day, but no further dose adjustment was allowed after the dose reduction.

Patients performed self-monitoring of fasting blood glucose every morning, or if they felt symptoms of hypoglycemia, and recorded the values in their diary. Treatment compliance was assessed by the investigator based on the patient diary, dispensed study drugs, number of collected study drugs, and number of lost study drugs. The use of glucose-lowering agents and insulin was prohibited, except for the use of ipragliflozin, GLP-1 receptor agonists, and SUs. In Japan, liraglutide is approved as monotherapy or as combination therapy with SUs, whereas other GLP-1 receptor agonists are approved for use only in combination with SUs. Because the Japanese clinical guidelines do not recommend any specific class of antidiabetic drug (including biguanides) as the first-line therapy, metformin was not included among the permitted concomitant oral antidiabetic drugs in this study. Temporary or topical use of corticosteroids or immunosuppressants was allowed.

Endpoints and Assessments

The changes from baseline (week 0) in HbA1c, FPG, fasting insulin, leptin, adiponectin, glucagon, body weight, waist circumference, homeostasis model assessment (HOMA)-R, HOMA-beta, and self-monitored blood glucose (SMBG) values recorded in the patient diary were examined. HbA1c, FPG, fasting insulin, leptin, adiponectin, and glucagon levels were measured by LSI Medience Corporation (Tokyo, Japan). For HbA1c levels, National Glycohemoglobin Standardization Program values were used. SMBG was performed seven times a day (fasting after waking up, 1 h after the start of breakfast, before lunch, 1 h after the start of lunch, before dinner, 1 h after the start of dinner, and before bedtime) for 3 days per week before each scheduled visit, and the measured value, time of measurement, start time of each meal, and dinner end time were recorded in the diary.

Safety was assessed in terms of vital signs, treatment-emergent adverse events (TEAEs), and laboratory tests. TEAEs were defined as AEs observed after the first administration of ipragliflozin and were classified according to system organ class and preferred term (MedDRA version 1.61; https://www.meddra.org/how-to-use/support-documentation); their relationship to the study drug, seriousness, and severity were evaluated.

Statistical Analysis

An estimated sample size of 100 patients (approximately 70 patients to receive ipragliflozin in combination with a GLP-1 receptor agonist and approximately 30 patients to receive ipragliflozin in combination with a GLP-1 receptor agonist and SU) was planned based on the Guidelines for Clinical Evaluation of Oral Antihyperglycemic Drugs (Notification no. 0709-1 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, dated July 9, 2010) [16], in which 50–100 patients per group are recommended to ensure a sufficient number of patients to evaluate the safety of the test drug.

The study analysis sets were the full analysis set (all patients who received at least one dose of ipragliflozin, and in whom at least one efficacy variable was measured after administration of ipragliflozin) and the safety analysis set (all patients who received at least one dose of ipragliflozin). Overall data were analyzed, and data for both subgroups separately: 50/50 mg group (in which the dose of ipragliflozin was maintained at week 20 because of sufficient efficacy or safety concerns) and the 50/100 mg group.

Missing data were not imputed, except for the month of T2DM diagnosis and partial onset dates of AEs. Baseline characteristics were summarized descriptively using mean ± standard deviation (SD) or the number and percentage of patients for continuous and categorical variables, respectively. Efficacy data were analyzed descriptively in terms of the mean ± SD values at each time point together with the mean

changes from baseline to each time point. The mean values and changes in efficacy variables from baseline to the end of treatment using the last observation carried forward were also calculated. TEAEs were presented as the number and percentage of patients in each treatment group. The statistical analyses were performed by Astellas Pharma Inc. using Version 9.2 or later of Windows SAS® (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patients

The baseline characteristics of patients are shown in Table 1. Overall, the majority of patients were male (72/103, 69.9%), had a mean (± SD) age of 53.4 ± 10.5 years at the time of consent, BMI of 28.09 ± 4.15 kg/m^2, HbA1c of 8.81 ± 0.89%, FPG of 185.9 ± 44.2 mg/dL, and estimated glomerular filtration rate of 86.69 ± 18.39 mL/min/1.73 m^2. More than one-half of the patients (57 [55.3%]) had diabetes for < 120 months (10 years). The majority (90/103 [87.4%]) had been treated with liraglutide monotherapy, with only 13/103 (12.6%) treated with liraglutide or another GLP-1 receptor agonist in combination with an SU. The percentage of patients who underwent washout of glucose-lowering agents other than GLP-1 receptor agonists and SU agents was 18.4% (19/103). When both groups were compared, the 50/50 mg group had numerically lower baseline body weight, BMI, FPG, and HbA1c values, and shorter diabetes mellitus duration compared with the 50/100 mg group.

As shown in the patient flow diagram (Fig. 2), a total of 103 patients received ipragliflozin 50 mg/day, three of whom discontinued the treatment by week 20 because of an AE, and 100 of whom continued ipragliflozin 50 mg/day until week 20. Of these, 67 patients had not achieved adequate glycemic control, and their ipragliflozin dose was increased to 100 mg/day (50/100 mg group), while 33 patients maintained the initial ipragliflozin dose (50/50 mg group). Among patients in the 50/50 mg group, 32 completed the study, and one patient discontinued because of lack of efficacy. Among those in the 50/100 mg group, two patients underwent a dose decrease to 50 mg/day after week 20 because of AEs (one patient presented fatigue and the other, pollakiuria); both patients completed the study. Of the remaining 65 patients in the 50/100 mg group, 49 patients completed the study and 16 discontinued (14 for lack of efficacy, 1 for an adverse event, and 1 patient withdrew voluntarily).

HbA1c, FPG, and SMBG

The mean (± SD) change in HbA1c from baseline to end of treatment was − 0.92 ± 0.80% (95% confidence interval [CI] − 1.07, − 0.76]) in all ipragliflozin-treated patients (n = 103). The mean changes in HbA1c from baseline to week 20 and from baseline to end of treatment were − 1.18 ± 0.66% and − 0.84 ± 0.75%, respectively, in the 50/50 mg group and − 0.95 ± 0.71% and − 0.97 ± 0.83%, respectively, in the 50/100 mg group (Table 2). These values reflect an increase of 0.33% from week 20 to end of treatment in the 50/50 mg group, but a decrease of 0.02% in the 50/100 mg group.

The time courses of HbA1c and changes in HbA1c from baseline in each dose subgroup are shown in Fig. 3a, b. The 50-mg dose was administered until week 20, and HbA1c decreased in both subgroups. In the 50/50 mg group, the dose remained at 50 mg/day at week 20, and HbA1c slightly increased until week 52. In the 50/100 mg group, the dose was increased to 100 mg/day at week 20, and HbA1c further decreased until week 36, with a subsequent slight increase until week 52.

The mean (± SD) change in FPG from baseline to the end of treatment was − 38.9 ± 39.0 mg/dL (95% CI − 46.5, − 31.3) (Table 2). The time courses of FPG and changes in FPG from baseline in each dose subgroup are shown in Fig. 4a, b. In each dose subgroup, FPG decreased rapidly within 2 weeks of starting treatment with ipragliflozin. In the 50/50 mg group, the FPG level continued to decrease gradually up to week 20 and remained almost unchanged thereafter. In the 50/100 mg group, the FPG level continued to decrease gradually

Table 1 Baseline characteristics

Baseline characteristics	All patients (n = 103)	50 mg/50 mg subgroup (n = 33)[a]	50 mg/100 mg subgroup (n = 67)[a]
Sex			
Male	72 (69.9)	25 (75.8)	46 (68.7)
Female	31 (30.1)	8 (24.2)	21 (31.3)
Age (years)	53.4 ± 10.5	51.8 ± 12.2	54.0 ± 9.4
< 65	82 (79.6)	26 (78.8)	54 (80.6)
≥ 65	21 (20.4)	7 (21.2)	13 (19.4)
Body weight (kg)	78.68 ± 16.45	76.46 ± 17.38	79.95 ± 16.14
Height (cm)	166.68 ± 9.17	166.75 ± 9.07	167.06 ± 9.12
BMI (kg/m^2)	28.09 ± 4.15	27.25 ± 4.52	28.42 ± 3.99
Duration of DM (months)	121.4 ± 74.7	116.6 ± 69.4	124.2 ± 76.6
< 120	57 (55.3)	18 (54.5)	37 (55.2)
≥ 120	46 (44.7)	15 (45.5)	30 (44.8)
Concomitant glucose-lowering agent			
Liraglutide monotherapy	90 (87.4)	27 (81.8)	60 (89.6)
GLP-1RA and SU agent[b]	13 (12.6)	6 (18.2)	7 (10.4)
Tobacco history			
Never used tobacco	42 (40.8)	17 (51.5)	22 (32.8)
Former tobacco user	32 (31.1)	8 (24.2)	24 (35.8)
Current tobacco user	29 (28.2)	8 (24.2)	21 (31.3)
Alcohol history			
Never used alcohol	33 (32.0)	5 (15.2)	26 (38.8)
Former alcohol user	4 (3.9)	1 (3.0)	3 (4.5)
Current alcohol user	66 (64.1)	27 (81.8)	38 (56.7)
Quantity level for current alcohol user[c]			
Level 1	48 (72.7)	21 (77.8)	26 (68.4)
Level 2	14 (21.2)	6 (22.2)	8 (21.1)
Level 3	4 (6.1)	0	4 (10.5)
Implementation of washout[d]			
No	84 (81.6)	28 (84.8)	54 (80.6)
Yes	19 (18.4)	5 (15.2)	13 (19.4)
HbA1c level (%)	8.81 ± 0.89	8.40 ± 0.59	9.02 ± 0.94
FPG (mg/dL)	185.9 ± 44.2	170.4 ± 28.8	192.9 ± 48.6

Table 1 continued

Baseline characteristics	All patients (n = 103)	50 mg/50 mg subgroup (n = 33)[a]	50 mg/100 mg subgroup (n = 67)[a]
C-peptide (ng/mL)	2.24 ± 1.10	2.20 ± 1.51	2.24 ± 0.84
eGFR (mL/min/1.73 m^2)	86.69 ± 18.39	87.35 ± 17.41	86.67 ± 19.22
< 90	62 (60.2)	20 (60.6)	40 (59.7)
≥ 90	41 (39.8)	13 (39.4)	27 (40.3)
SBP (mmHg)	133.4 ± 16.3	131.6 ± 14.5	133.4 ± 17.0
DBP (mmHg)	83.4 ± 11.9	83.5 ± 9.8	83.0 ± 12.5
12-lead ECG			
Normal	84 (81.6)	27 (81.8)	55 (82.1)
Abnormal: not clinically significant	18 (17.5)	5 (15.2)	12 (17.9)
Abnormal: clinically significant	1 (1.0)	1 (3.0)	0

Values are presented as the number (n) with the percentage in parentheses or as the mean ± standard deviation (SD)
BMI Body mass index, *DBP* diastolic blood pressure, *DM* diabetes mellitus, *ECG* electrocardiogram, *eGFR* estimated glomerular filtration rate, *FPG* fasting plasma glucose, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *HbA1c* hemoglobin A1c, *SBP* systolic blood pressure, *SU* sulfonylurea

[a] At the beginning of the 20-week open-label treatment period, all patients received 50 mg/day of ipragliflozin. At week 20, the ipragliflozin dose could be increased to 100 mg/day in patients, or not, yielding the 50 mg/100 mg and 50 mg/50 mg subgroups, respectively

[b] 12 patients were receiving liraglutide + SU and one patient was receiving exenatide + SU

[c] Level of alcohol consumption (daily) was categorized as: Level 1: < 1 medium-sized bottle of beer, < 1 go (180.39 mL) of sake, < 60 mL of whiskey/brandy, < 90 mL of shochu (35%), and < 240 mL of wine; Level 2: 1 to < 3 medium-sized bottles of beer, 1 to < 3 go (180.39–541.17 mL) of sake, 60 to < 180 mL of whiskey/brandy, 90 to < 270 mL of shochu (35%), and 240 to < 720 mL of wine; Level 3: ≥ 3 medium-sized bottles of beer, ≥ 3 go (541.17 mL) of sake, ≥ 180 mL of whiskey/brandy, ≥ 270 mL of shochu (35%), and ≥ 720 mL of wine

[d] If patients had concomitantly received hypoglycemic agents other than GLP-1RA and SU agents, washout of these agents was performed: (1) for patients receiving liraglutide monotherapy, glucose-lowering agents other than liraglutide, and (2) for patients receiving combination therapy with liraglutide or other GLP-1RA + SU agent, glucose-lowering agents other than GLP-1RA and SU agents

up to week 32 and remained almost unchanged thereafter. The decrease in FPG until week 52 was more marked in the 50/100 mg group.

The mean (± SD) change in SMBG from baseline to the end of treatment in all patients was − 38.9 ± 41.3 mg/dL in the fasting state, − 52.5 ± 61.2 mg/dL 1 h after breakfast, − 47.3 ± 53.5 mg/dL before lunch, − 51.3 ± 69.1 mg/dL 1 h after lunch, − 35.9 ± 46.8 mg/dL before dinner, − 40.9 ± 63.7 mg/dL 1 h after dinner, and − 54.9 ± 65.3 mg/dL before bedtime (Table 2). Figure 5 shows the SMBG profile in each dose subgroup. A sustained reduction from baseline in SMBG was observed over the 52 weeks of treatment in both ipragliflozin dose subgroups at all measurement time points. The same sustained reduction in SMBG was reflected by the changes in the seven-point SMBG profile from baseline to the end of treatment in both ipragliflozin dose subgroups, as shown in Fig. 6.

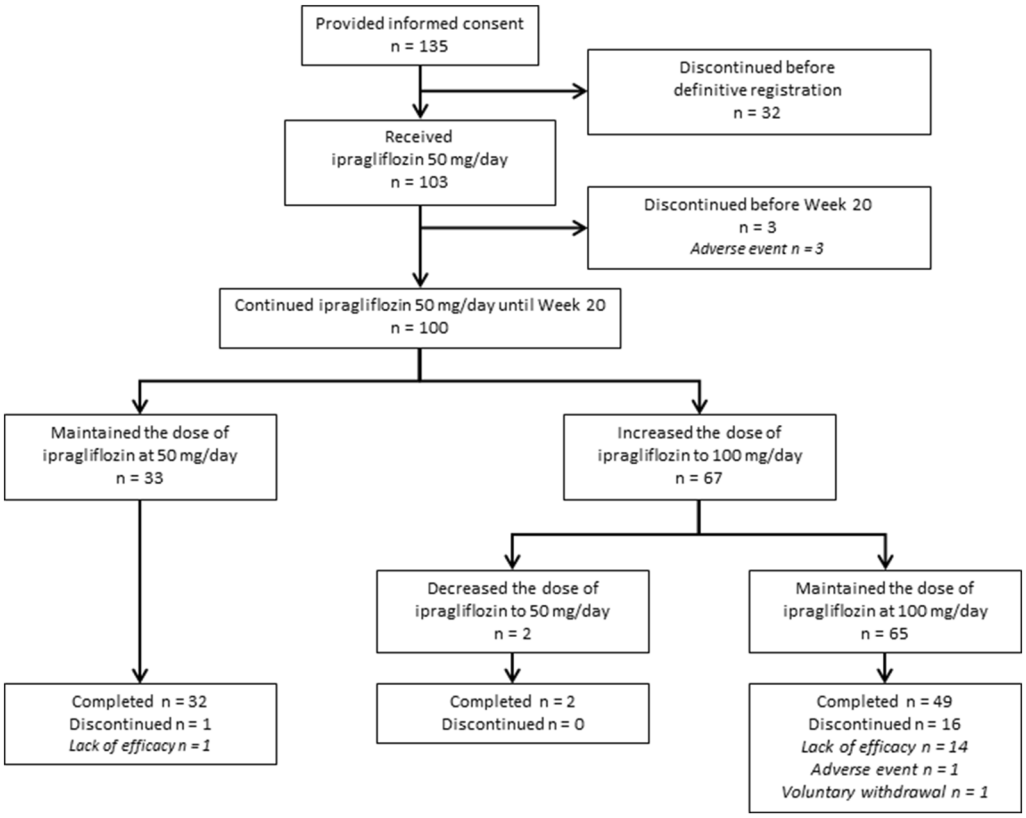

Fig. 2 Flow chart of patient disposition during the study

Metabolic Parameters

Table 2 shows the changes in body weight, waist circumference, and metabolic parameters from baseline to the end of treatment in all ipragliflozin-treated patients and according to the dose of ipragliflozin used. The mean (SD) change in body weight from baseline to the end of treatment in all patients was − 2.69 ± 2.39 kg (95% CI − 3.16, − 2.22). The mean change in body weight from baseline to the end of treatment in the 50/50 mg group was − 2.53 ± 1.48 kg and that in the 50/100 mg group was − 2.77 ± 2.76 kg. The time courses of body weight and changes in body weight from baseline in each dose subgroup are shown in Fig. 7a, b. During the course of the 52-week treatment, body weight decreased progressively in each ipragliflozin dose subgroup. In the 50/50 mg group, a marked decline in body weight was observed up to week 16, after which it showed a tendency to increase, and then remained approximately stable up to week 52. In the 50/100 mg group, body weight declined more gradually, with a further reduction after the dose was increased to 100 mg/day at week 20.

Glucagon increased from baseline to the end of treatment; the increase was 23.1 ± 27.6 pg/mL (95% CI 17.7, 28.5) in all patients. Leptin was unchanged in all patients (− 0.19 ± 4.29 ng/mL; 95% CI − 1.03, 0.65). Adiponectin increased in all patients (0.98 ± 1.63 μg/mL; 95% CI 0.66, 1.30) (Table 2).

Safety

Treatment-emergent adverse events occurring in all patients who received ipragliflozin are shown in Table 3. TEAEs occurred in 77.7% (80/103) of patients treated with ipragliflozin. Overall, 46.6% (48/103) of patients experienced drug-related TEAEs. Serious TEAEs occurred in

Table 2 Efficacy variables

Variables	Baseline values, values at specific time points, and mean change	All patients (n = 103)	50 mg/50 mg (n = 33)	50 mg/100 mg (n = 67)
HbA1c (%)	Baseline	8.81 ± 0.89	8.40 ± 0.59	9.02 ± 0.94
	Week 20/change	7.80 ± 0.82 (101)/− 1.03 ± 0.70 (101)	7.22 ± 0.67/− 1.18 ± 0.66	8.07 ± 0.75/− 0.95 ± 0.71
	EOT/change	7.90 ± 0.85/− 0.92 ± 0.80	7.56 ± 0.74/− 0.84 ± 0.75	8.06 ± 0.87/− 0.97 ± 0.83
	Change at EOT (95% CI)	− 0.92 (− 1.07, − 0.76)	NA	NA
FPG (mg/dL)	Baseline	185.9 ± 44.2	170.4 ± 28.8	192.9 ± 48.6
	Week 20/change	144.4 ± 22.6 (99)/− 41.2 ± 37.2 (99)	131.9 ± 16.1/− 38.5 ± 23.3	150.6 ± 22.8 (66)/− 42.5 ± 42.6 (66)
	EOT/change	147.0 ± 25.3/− 38.9 ± 39.0	143.8 ± 24.5/− 26.5 ± 28.1	148.4 ± 25.9/− 44.5 ± 42.4
	Change at EOT (95% CI)	− 38.9 (− 46.5, − 31.3)	NA	NA
SMBG (mg/dL)				
Fasting after waking up	Baseline	179.1 ± 51.1 (101)	158.6 ± 34.0	190.9 ± 54.2 (65)
	EOT/change at EOT	141.3 ± 27.1 (100)/− 38.9 ± 41.3 (98)	131.1 ± 21.62/− 27.6 ± 29.7	146.3 ± 28.2/− 44.6 ± 45.2 (65)
1 h after breakfast	Baseline	283.4 ± 61.8 (98)	266.2 ± 51.7	294.0 ± 63.5 (62)
	EOT/change at EOT	231.1 ± 54.5 (99)/− 52.5 ± 61.2 (94)	217.3 ± 57.3/− 48.9 ± 48.4	238.0 ± 52.1 (66)/− 54.5 ± 67.4 (61)
Before lunch	Baseline	183.6 ± 60.6 (101)	162.7 ± 45.2	194.9 ± 65.9 (65)
	EOT/change at EOT	137.6 ± 31.1 (99)/− 47.3 ± 53.5 (97)	126.0 ± 23.0 (32)/− 37.8 ± 37.7 (32)	143.2 ± 33.0/− 51.9 ± 59.5 (65)
1 h after lunch	Baseline	267.8 ± 72.0 (100)	247.1 ± 53.2 (33)	280.0 ± 78.7 (64)
	EOT/change at EOT	218.2 ± 42.5 (99)/− 51.3 ± 69.1 (96)	212.0 ± 44.3 (32)/− 35.2 ± 48.0 (32)	221.1 ± 41.7/− 59.3 ± 76.6 (64)
Before dinner	Baseline	177.0 ± 60.0 (100)	152.6 ± 44.5 (32)	189.1 ± 62.7 (65)
	EOT/change at EOT	141.2 ± 35.2 (99)/− 35.9 ± 46.8 (96)	128.1 ± 28.8 (32)/− 25.3 ± 33.2 (31)	147.5 ± 36.4/− 41.0 ± 51.5 (65)

Table 2 continued

Variables	Baseline values, values at specific time points, and mean change	All patients (n = 103)	50 mg/50 mg (n = 33)	50 mg/100 mg (n = 67)
1 h after dinner	Baseline	264.5 ± 69.7 (98)	235.7 ± 58.7	279.2 ± 71.1 (62)
	EOT/change at EOT	223.7 ± 47.6 (99)/− 40.9 ± 63.7 (94)	208.2 ± 48.9/− 27.5 ± 54.5	231.4 ± 45.3 (66)/− 48.1 ± 67.4 (61)
Before bedtime	Baseline	240.3 ± 78.4 (100)	201.4 ± 50.3	258.8 ± 82.7 (64)
	EOT/change at EOT	184.0 ± 48.1 (100)/− 54.9 ± 65.3 (97)	167.1 ± 35.3/− 34.2 ± 49.5	192.4 ± 51.5/− 65.5 ± 70.1 (64)
Body weight (kg)	Baseline	78.48 ± 16.33	76.40 ± 17.40	79.68 ± 15.94
	Week 20/change	75.95 ± 16.49 (101)/− 2.44 ± 1.63 (101)	73.96 ± 17.55/− 2.44 ± 1.28	77.28 ± 15.83/− 2.40 ± 1.77
	EOT/change	75.79 ± 16.36/− 2.69 ± 2.39	73.87 ± 17.38/− 2.53 ± 1.48	76.91 ± 15.96/− 2.77 ± 2.76
	Change at EOT (95% CI)	− 2.69 (− 3.16, − 2.22)	NA	NA
Waist circumference (cm)	Baseline	95.88 ± 10.31	93.68 ± 11.47	96.88 ± 9.80
	EOT/change	93.86 ± 10.72 (101)/− 1.94 ± 3.89 (101)	92.50 ± 12.26/− 1.18 ± 3.96	94.59 ± 9.97/− 2.29 ± 3.86
	Change at EOT (95% CI)	− 1.94 (− 2.71, − 1.17)	NA	NA
Glucagon (pg/mL)	Baseline	121.5 ± 23.5	121.7 ± 27.1	121.4 ± 22.0
	EOT/change	144.7 ± 31.7/23.1 ± 27.6	144.0 ± 23.2/22.3 ± 24.2	146.0 ± 35.6/24.6 ± 29.3
	Change at EOT (95% CI)	23.1 (17.7, 28.5)	NA	NA
Leptin (ng/mL)	Baseline	11.74 ± 9.17	9.60 ± 6.31	12.49 ± 10.25
	EOT/change	11.54 ± 7.59/− 0.19 ± 4.29	9.34 ± 6.28/− 0.26 ± 2.64	12.46 ± 8.10/− 0.03 ± 4.94
	Change at EOT (95% CI)	− 0.19 (− 1.03, 0.65)	NA	NA
Adiponectin (μg/mL)	Baseline	6.15 ± 2.99	6.13 ± 2.88	6.12 ± 3.08
	EOT/change	7.13 ± 3.58/0.98 ± 1.63	7.43 ± 3.78/1.30 ± 1.55	6.98 ± 3.54/0.86 ± 1.68
	Change at EOT (95% CI)	0.98 (0.66, 1.30)	NA	NA

Table 2 continued

Variables	Baseline values, values at specific time points, and mean change	All patients (n = 103)	50 mg/50 mg (n = 33)	50 mg/100 mg (n = 67)
Fasting insulin (mIU/L)	Baseline	14.06 ± 16.35	13.79 ± 14.94	14.13 ± 17.39
	EOT/change	10.59 ± 9.35/− 3.47 ± 11.39	10.94 ± 9.96/− 2.85 ± 14.58	10.34 ± 9.29/− 3.79 ± 9.82
	Change at EOT (95% CI)	− 3.47 (− 5.70, − 1.24)	NA	NA
HOMA-R	Baseline	6.87 ± 9.60	6.45 ± 9.62	7.07 ± 9.85
	EOT/change	3.95 ± 3.90/− 2.92 ± 7.92	4.17 ± 4.92/− 2.28 ± 9.45	3.81 ± 3.42/− 3.25 ± 7.29
	Change at EOT (95% CI)	− 2.92 (− 4.47, − 1.37)	NA	NA
HOMA-beta	Baseline	42.5 ± 39.0	43.6 ± 30.9	41.7 ± 43.1
	EOT/change	47.4 ± 38.8/4.9 ± 19.7	48.1 ± 31.4/4.4 ± 27.3	46.7 ± 42.7/5.0 ± 15.1
	Change at EOT (95% CI)	4.9 (1.0, 8.7)	NA	NA

Values are presented as the mean ± SD

Where the number of patients differed from the number of patients in the full analysis set, the number is given in parentheses

CI Confidence interval, *EOT* end of the treatment period, *HOMA* homeostasis model assessment, *NA* not analyzed, *SMBG* self-monitored blood glucose

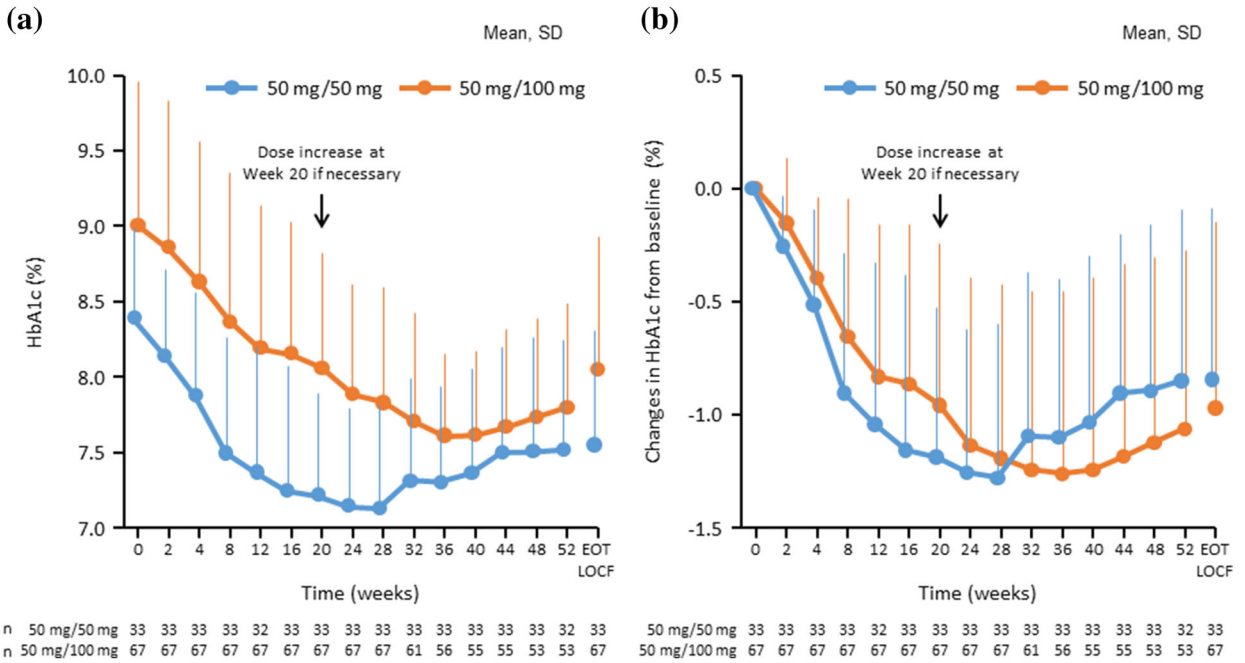

Fig. 3 **a** Time course of glycosylated hemoglobin (*HbA1c*) of patients in each dose subgroup, **b** time course of changes in HbA1c from baseline to end of treatment of patients in each dose subgroup. Data are shown as the mean and standard deviation (*SD*) (full analysis set) for all patients who received ipragliflozin. Error bars: SD. The number of patients at each time point is shown below the *x*-axis. *EOT* End of the treatment period, *LOCF* last observation carried forward

3.9% (4/103) of patients and included glaucoma, nasopharyngitis, cerebral infarction, and sleep apnea syndrome (in one patient each). Hospitalization was required in three cases (glaucoma, nasopharyngitis, and sleep apnea syndrome), and cerebral infarction was regarded as an event of medical significance. Of these, glaucoma and nasopharyngitis were considered by the investigator as not related to the study drug. TEAEs leading to permanent discontinuation occurred in 3.9% (4/103) of patients and included constipation, hypoglycemia, cerebral infarction, and rash (in one patient each). The latter patient developed a rash on day 29 after starting treatment, which disappeared completely (resolved) by day 50. The patient continued medical treatment for the rash up to day 47. The severity of the rash was mild, and it was considered as "probably related" to the study treatment. By preferred term, the most common drug-related TEAEs in all patients were pollakiuria (9.7% [10/103]), hypoglycemia (8.7% [9/103]), constipation (6.8% [7/103]), and thirst (5.8% [6/103]). Administration of ipragliflozin was not associated with any clinically significant changes in laboratory variables or vital signs, except for increased blood ketone bodies. No deaths were reported during this study.

DISCUSSION

Given the lack of efficacy and safety data on ipragliflozin when used in combination with GLP-1 receptor agonists for the treatment of T2DM in Japan, we conducted this open-label, clinical study to evaluate the efficacy and safety of ipragliflozin treatment (52 weeks, 50 or 100 mg/day) in combination with GLP-1 receptor agonists. We also assessed the persistence of the efficacy of treatment with ipragliflozin 50 mg/day and the effect of a dose increase of ipragliflozin to 100 mg/day in this patient sample.

The improvement in glycemic control in patients treated with ipragliflozin was

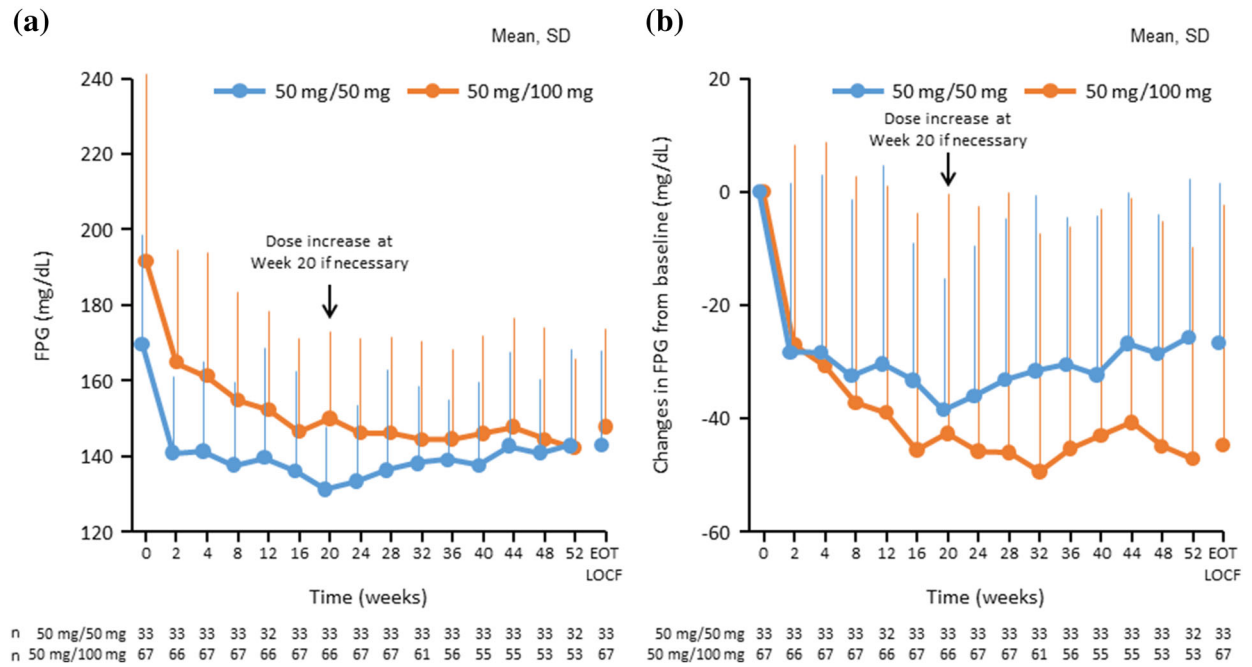

Fig. 4 **a** Time course of fasting plasma glucose (*FPG*) of patients in each dose subgroup, **b** time course of changes in FPG from baseline to end of treatment of patients in each dose subgroup. Data are shown as the mean and SD (full analysis set) for all patients who received ipragliflozin. Error bars: SD. The number of patients at each time point is shown below the *x*-axis

maintained from baseline up to week 52. The mean HbA1c and FPG levels decreased immediately after initiation of the study treatment, and the lowered values were sustained until week 52. Consistent with these observations, a sustained reduction from baseline in SMBG was observed over 52 weeks for all time points, which indicates that ipragliflozin exhibits glucose-lowering effects on both fasting and postprandial blood glucose levels. These results are consistent with those of previous clinical trials of ipragliflozin alone or in combination with other oral glucose-lowering agents [8–13, 17–19].

Mean body weight steadily decreased from baseline up to week 16, and the decrease was maintained throughout the 52-week treatment. This is a relevant clinical finding because weight gain is a shortcoming of several existing therapies for diabetes, including insulin [5]. Weight reduction is a strength of GLP-1 receptor agonist therapy [20]. However, in this study, this weight-reducing effect was further reinforced by the use of ipragliflozin, which promotes urinary calorie loss [21]. These effects on glycemic control and body weight are consistent with the results of recent studies on dapagliflozin [22] and luseogliflozin [23] added on to therapy with a GLP-1 receptor agonist in Japanese patients. The use of concomitant SUs in some patients may have influenced the evaluations of weight change. However, because the number of patients in this group was limited (13 patients), a separate subanalysis of body weight change in this group was not performed.

In the present study, we further showed that the dose increase of ipragliflozin to 100 mg/day resulted in better glycemic control and weight reduction in patients for whom the 50-mg dose was insufficient. Absolute reductions in either HbA1c or body weight were larger in patients in the 50/100 mg group than in those in the 50/50 mg group. This may be the result of differences in baseline HbA1c and body weight. Nonetheless, HbA1c and body weight were maintained in the 50/100 group compared with the tendency of these parameters to increase in the 50/50 group after 20 weeks. This finding

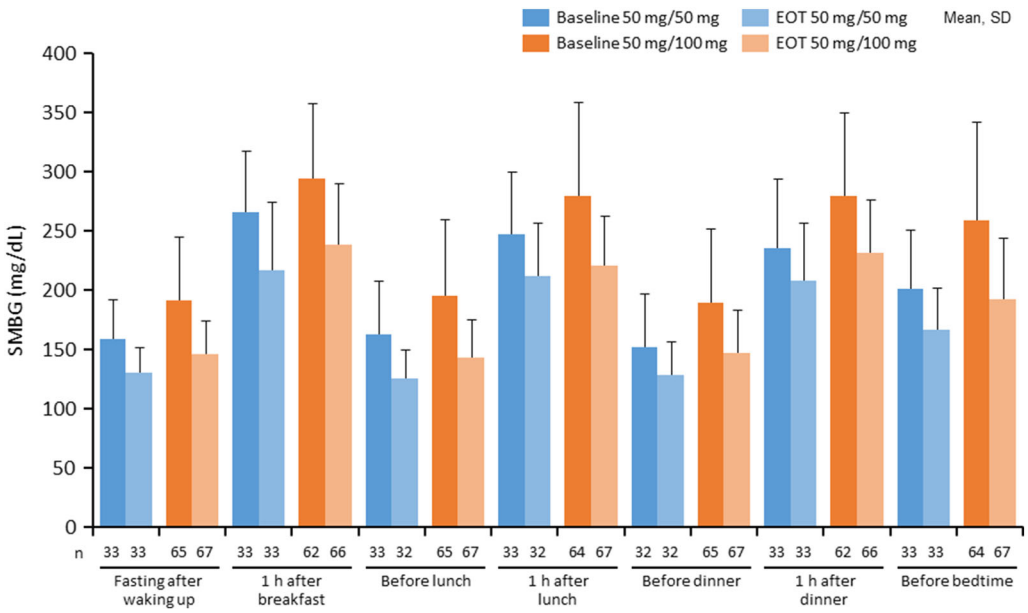

Fig. 5 Seven-point self-monitored blood glucose (*SMBG*) profile at baseline and EOT in each dose subgroup. Error bars: SD

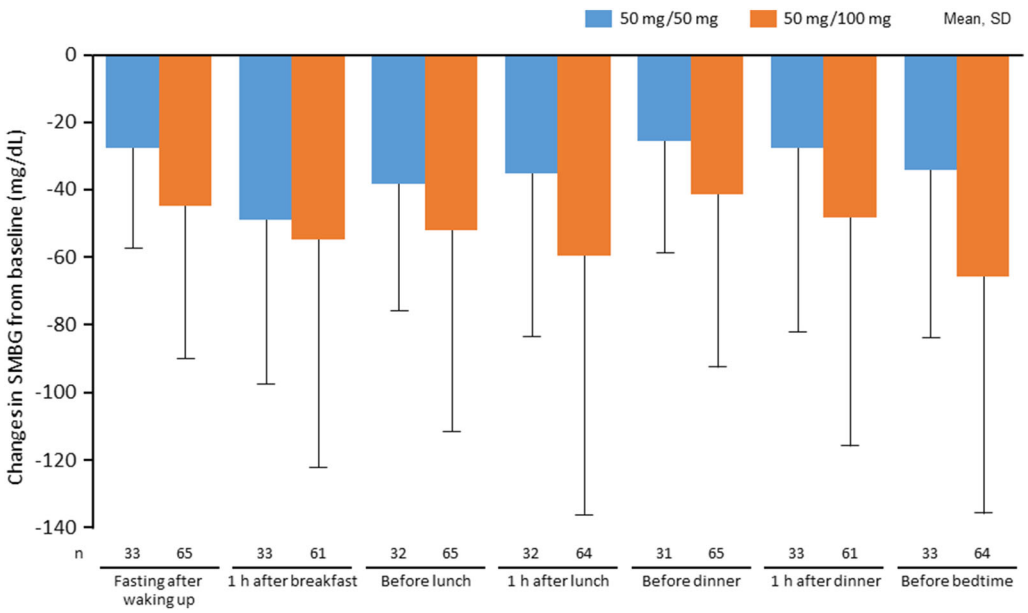

Fig. 6 Changes in seven-point SMBG profile from baseline to end of treatment in each dose subgroup. Error bars: SD

suggests that increasing the ipragliflozin dose to 100 mg/day is a feasible option when sufficient glycemic control or weight reduction is not achieved after several months of treatment with ipragliflozin 50 mg/day.

In terms of safety, the incidence of TEAEs was 77.7% (80/103) and that of drug-related TEAEs was 46.6% (48/103); all TEAEs were mild or moderate in severity. The rate of serious TEAEs was low (4 patients [3.9%]), and all serious TEAEs were mild in severity.

As the pharmacological action of ipragliflozin involves increased urinary glucose excretion, particular attention was focused on

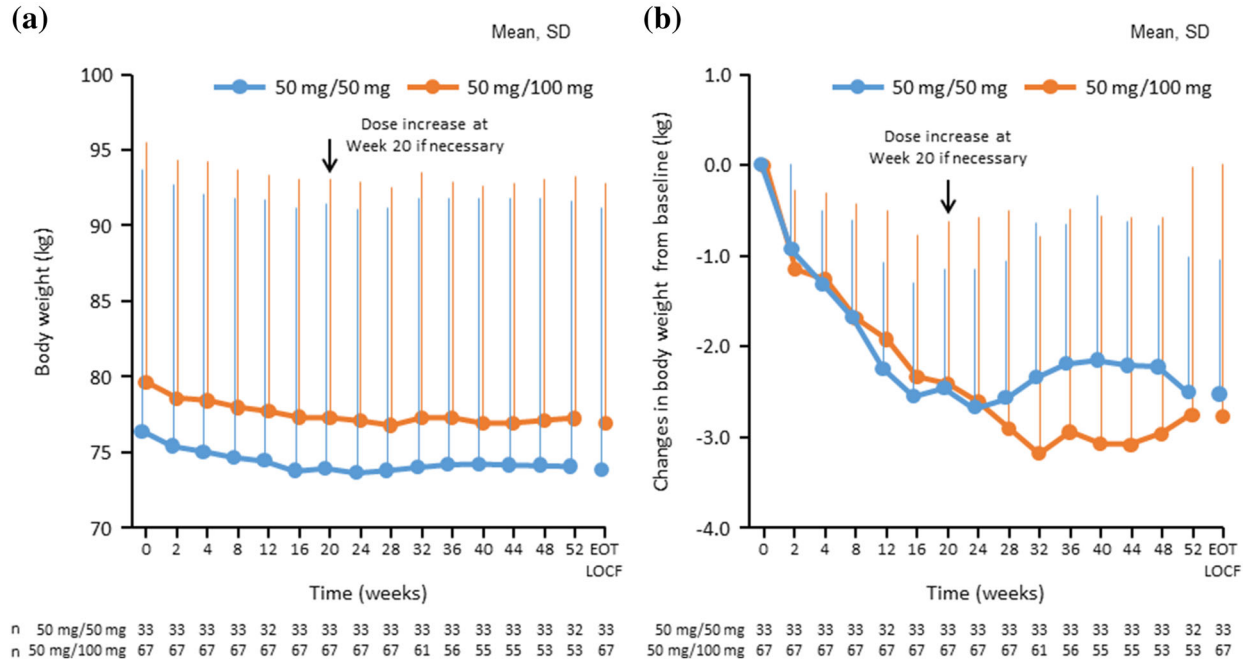

Fig. 7 **a** Time course of body weight of patients in each dose subgroup, **b** time course of changes in body weight from baseline to end of treatment of patients in each dose subgroup. Data are shown as the mean and SD (full analysis set) for all patients who received ipragliflozin. Error bars: SD. The number of patients at each time point is shown below the *x*-axis

hypoglycemia, urinary tract infection, genital infection, and effects on body fluid volume and electrolytes. These events were noted, but all were mild in severity and resolved without the need for specific treatment. Of the nine patients who experienced hypoglycemia-related events, only one had to permanently discontinue the study.

The most common drug-related TEAEs were pollakiuria, hypoglycemia, constipation, and thirst. The gastrointestinal drug-related TEAEs reported are in line with the characteristics of GLP-1 receptor agonist therapy; these typically include nausea in approximately 15–20% of patients, as well as vomiting, constipation, and diarrhea (approx. 5% each) [24]. The TEAEs that did occur in the present study have been previously reported in other clinical trials of ipragliflozin [8–13, 17, 19]. Although we did not observe any striking differences in the incidence of TEAEs between our study and previous clinical trials, we did note fewer cases of cystitis and more cases of thirst. Although SGLT2 inhibitors have been associated with urinary tract infections in some studies, this finding is not consistent among all trials [24]. The lower incidence observed in our study compared with others may be attributed to cultural differences in the Japanese lifestyle, such as bathing practices. Similarly, the incidence of thirst may have been influenced by the hot and humid summer weather in Japan. In summary, no previously unreported TEAEs were found when ipragliflozin was used in combination with GLP-1 receptor agonists.

A recently published review article by DeFronzo [24] discussed the potential benefits of the combined use of SGLT2 inhibitors and GLP-1 receptor agonists on metabolic–cardiovascular–renal disease in patients with T2DM. Such benefits of this combination therapy may outweigh the resulting AEs, which in this study were mostly mild in severity. However, further safety data are required to determine whether the observed AEs are a result of a class effect.

This study had several limitations, such as the open-label study design and consequent lack of a control group. Additionally, all

Table 3 Treatment-emergent adverse events

TEAEs	All patients (n = 103)
Total TEAEs	80 (77.7)
Serious TEAEs	4 (3.9)
TEAEs leading to permanent discontinuation	4 (3.9)
Total drug-related[a] TEAEs	48 (46.6)
Drug-related[a] serious TEAEs	2 (1.9)
Drug-related[a] TEAEs leading to permanent discontinuation	4 (3.9)
All drug-related TEAEs	
Hypoglycemia	9 (8.7)
Blood ketone body increased	3 (2.9)
Cystitis	2 (1.9)
Urine output increased	1 (1.0)
Hematuria	1 (1.0)
Pollakiuria	10 (9.7)
Urethral disorder	1 (1.0)
Balanoposthitis	1 (1.0)
Pruritus genital	4 (3.9)
Dermal cyst	1 (1.0)
Eczema	1 (1.0)
Pruritus	1 (1.0)
Rash	3 (2.9)
Abdominal discomfort	1 (1.0)
Abdominal distension	1 (1.0)
Constipation	7 (6.8)
Gastritis	1 (1.0)
Gastritis atrophic	1 (1.0)
Gastroesophageal reflux disease	1 (1.0)
Hemorrhagic erosive gastritis	1 (1.0)
Nausea	1 (1.0)
Fatigue	1 (1.0)
Hunger	1 (1.0)
Thirst	6 (5.8)
Dizziness	1 (1.0)
Dizziness postural	1 (1.0)
Headache	2 (1.9)
Insomnia	1 (1.0)
Polycythemia	1 (1.0)
Tachycardia	1 (1.0)
Gout	1 (1.0)
Cerebral infarction	1 (1.0)
Cervicobrachial syndrome	1 (1.0)
Sleep apnea syndrome	1 (1.0)

TEAE Treatment-emergent adverse event
Coded by MedDRA Ver. 16.1. Data are shown as the number (n) of patients, with the percentage in parentheses
[a] Relationship to ipragliflozin was possible, probable, or unknown, as assessed by the investigator

analyses reported here were performed in an exploratory manner, without formal statistical tests. The present results can only be generalized to the Japanese T2DM population, and there are some inconsistencies between Japanese and international guidelines in the recommended drugs for the treatment of type 2 diabetes. A high proportion of patients completed the study, which may be a reflection of the benefits of SGLT2 inhibitors (e.g., weight loss and glycemic improvement) during the treatment of type 2 diabetes.

Ipragliflozin treatment for 52 weeks in combination with a GLP-1 receptor agonist was found to be clinically and significantly efficacious in reducing HbA1c, FPG, and SMBG in patients with type 2 diabetes who had inadequate glycemic control with GLP-1 receptor agonist therapy. The mean body weight steadily decreased from baseline up to week 16, and the

decrease was maintained until the end of the treatment. Increasing the daily dose of ipragliflozin to 100 mg led to better glycemic control in patients for whom efficacy was insufficient at a dose of 50 mg. No previously unreported safety concerns were identified.

CONCLUSIONS

The results from this study suggest that ipragliflozin can be recommended as a well-tolerated and effective add-on therapy to a GLP-1 receptor agonist for glycemic control in T2DM patients. Because both SGLT2 inhibitors [25] and GLP-1 receptor agonists [26] have been shown to be beneficial for cardiovascular risks, this combination therapy could be a favorable choice for treatment of T2DM.

ACKNOWLEDGEMENTS

The authors wish to thank all of the investigators involved in this trial.

Funding. This study was sponsored by Astellas Pharma Inc., Tokyo, Japan. Article processing charges were also funded by Astellas Pharma Inc., Tokyo, Japan. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Medical Writing, Editorial and Other Assistance. Medical writing and editorial support was provided by Dr Keyra Martinez Dunn (Edanz Medical Writing) and Elsevier/ELM-COM™ and was funded by Astellas Pharma Inc.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. HI and TS contributed to study design, data analysis, and writing of the manuscript. SY and IN contributed to study design, study conduct, data collection and analysis, and writing of the manuscript.

Disclosures. Hisamitsu Ishihara has served on the scientific advisory board of Astellas Pharma Inc., received lecture or consulting fees from Astellas Pharma Inc., MSD, Sanofi, Mitsubishi Tanabe Pharma, Boehringer Ingelheim Japan, and Novartis Pharma, and received grants/research support from Astellas Pharma Inc., Ono Pharmaceutical, Boehringer Ingelheim Japan, AstraZeneca, Sanofi, Mitsubishi Tanabe Pharma, Eli Lilly Japan, Daiichi-Sankyo, Novo Nordisk Pharma, Kyowa Hakko Kirin, and MSD. Susumu Yamaguchi is an employee of Astellas Pharma Inc., Japan. Ikko Nakao is an employee of Astellas Pharma Inc., Japan. Taishi Sakatani is an employee of Astellas Pharma Inc., Japan.

Compliance with Ethics Guidelines. All procedures performed in the study were in accordance with the ethical standards of the institutional review board of each site and with the 1964 Helsinki declaration and its later amendments. Additionally, the study complied with all relevant laws and regulations, including Good Clinical Practice and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines. Informed consent was obtained from all individual participants included in the study.

Data Availability. The study synopsis, including the actual study results, can be found at http://www.astellasclinicalstudyresults.com. Access to anonymized individual patient-level data will be organized using the CSDR system at http://www.clinicalstudydatarequest.com. Requests will be reviewed by an independent panel. For approved requests, access will be granted after a data-sharing agreement has been signed.

REFERENCES

1. Malik VS, Willett WC, Hu FB. Global obesity: trends, risk factors and policy implications. Nat Rev Endocrinol. 2013;9:13–27.

2. Mozaffarian D. Foods, obesity, and diabetes—are all calories created equal? Nutr Rev. 2017;75[Suppl 1]:19–31.

3. Bell DS. Type 2 diabetes mellitus: what is the optimal treatment regimen? Am J Med. 2004;116[Suppl 5A]:23–9.

4. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA. 2004;291:335–42.

5. Bolen S, Feldman L, Vassy J, et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med. 2007;147:386–99.

6. Abdul-Ghani MA, Norton L, DeFronzo RA. Efficacy and safety of SGLT2 inhibitors in the treatment of type 2 diabetes mellitus. Curr Diabetes Rep. 2012;12:230–8.

7. Isaji M. SGLT2 inhibitors: molecular design and potential differences in effect. Kidney Int Suppl. 2011;79[Suppl 120]:S14–9.

8. Kadokura T, Akiyama N, Kashiwagi A, et al. Pharmacokinetic and pharmacodynamic study of ipragliflozin in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled study. Diabetes Res Clin Pract. 2014;106:50–6.

9. Kashiwagi A, Akiyama N, Shiga T, et al. Efficacy and safety of ipragliflozin as an add-on to a sulfonylurea in Japanese patients with inadequately controlled type 2 diabetes: results of the randomized, placebo-controlled, double-blind, phase III EMIT study. Diabetol Int. 2015;6:125–38.

10. Kashiwagi A, Kazuta K, Goto K, Yoshida S, Ueyama E, Utsuno A. Ipragliflozin in combination with metformin for the treatment of Japanese patients with type 2 diabetes: ILLUMINATE, a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2015;17:304–8.

11. Kashiwagi A, Kazuta K, Takinami Y, Yoshida S, Utsuno A, Nagase I. Ipragliflozin improves glycemic control in Japanese patients with type 2 diabetes mellitus: the BRIGHTEN study. Diabetol Int. 2015;6:8–18.

12. Kashiwagi A, Shiga T, Akiyama N, et al. Efficacy and safety of ipragliflozin as an add-on to pioglitazone in Japanese patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebo-controlled study (the SPOTLIGHT study). Diabetol Int. 2015;6:104–16.

13. Kashiwagi A, Takahashi H, Ishikawa H, et al. A randomized, double-blind, placebo-controlled study on long-term efficacy and safety of ipragliflozin treatment in patients with type 2 diabetes mellitus and renal impairment: results of the long-term ASP1941 safety evaluation in patients with type 2 diabetes with renal impairment (LANTERN) study. Diabetes Obes Metab. 2015;17:152–60.

14. Lovshin JA. Glucagon-like peptide-1 receptor agonists: a class update for treating type 2 diabetes. Can J Diabetes. 2017;S1499–S2671:30532–9.

15. American Diabetes Association. Executive summary: standards of medical care in diabetes—2014. Diabetes Care. 2014;37(Suppl 1):5–13.

16. Pharmaceuticals and Medical Devices Agency (2010) On release of the Guideline for Clinical Evaluation of Oral Antihyperglycemic Agents. Notification No. 0709-1 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau. https://www.pmda.go.jp/files/000208194.pdf. Accessed 25 Apr 2018.

17. Wilding JP, Ferrannini E, Fonseca VA, Wilpshaar W, Dhanjal P, Houzer A. Efficacy and safety of ipragliflozin in patients with type 2 diabetes inadequately controlled on metformin: a dose-finding study. Diabetes Obes Metab. 2013;15:403–9.

18. Fonseca VA, Ferrannini E, Wilding JP, et al. Active- and placebo-controlled dose-finding study to assess the efficacy, safety, and tolerability of multiple doses of ipragliflozin in patients with type 2 diabetes mellitus. J Diabetes Complicat. 2013;27:268–73.

19. Lu CH, Min KW, Chuang LM, Kokubo S, Yoshida S, Cha BS. Efficacy, safety, and tolerability of ipragliflozin in Asian patients with type 2 diabetes mellitus and inadequate glycemic control with metformin: results of a phase 3 randomized, placebo-controlled, double-blind, multicenter trial. J Diabetes Investig. 2016;7:366–73.

20. Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ. 2012;344:d7771.

21. Kurosaki E, Ogasawara H. Ipragliflozin and other sodium-glucose cotransporter-2 (SGLT2) inhibitors in the treatment of type 2 diabetes: preclinical and clinical data. Pharmacol Ther. 2013;139:51–9.

22. 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;5:415–33.

23. Seino Y, Yabe D, Sasaki T, et al. Sodium-glucose cotransporter-2 inhibitor luseogliflozin added to glucagon-like peptide 1 receptor agonist liraglutide improves glycemic 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;9:332–40.

24. DeFronzo RA. Combination therapy with GLP-1 receptor agonist and SGLT2 inhibitor. Diabetes Obes Metab. 2017;19:1353–62.

25. Rastogi A, Bhansali A. SGLT2 inhibitors through the windows of EMPA-REG and CANVAS trials: a review. Diabetes Ther. 2017;8:1245–51.

26. Bethel MA, Patel RA, Merrill P, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. Lancet Diabetes Endocrinol. 2018;6:105–13.