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CLINICAL TRIAL

Long-term (52-week) efficacy and safety of ipragliflozin add-on therapy to insulin in Japanese patients with type 1 diabetes mellitus: An uncontrolled, open-label extension of a phase III study

Kohei Kaku[1]*, Hiroyuki Isaka[2], Taishi Sakatani[3], Junko Toyoshima[4]

[1]Department of Medicine, Kawasaki Medical School, Okayama, Japan, [2]Japan/Asia Clinical Development, Astellas Pharma Inc., Tokyo, Japan, [3]Data Science, Astellas Pharma Inc., Tokyo, Japan, and [4]Clinical Pharmacology and Exploratory Development, Astellas Pharma Inc., Tokyo, Japan

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***Correspondence**
Kohei Kaku
Tel.: +81-86-462-1111
Fax: +81-86-462-7897
E-mail address:
kka@med.kawasaki-m.ac.jp

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ABSTRACT

Introduction: The aim of the present study was to assess the long-term (52-week) efficacy and safety of ipragliflozin in insulin-treated Japanese patients with type 1 diabetes mellitus and inadequate glycemic control.

Materials and Methods: In this 28-week, open-label extension of a multicenter, randomized, placebo-controlled, 24-week phase III study, ipragliflozin recipients continued treatment (50 mg, once daily), and placebo recipients were switched to once-daily 50 mg ipragliflozin at the start of the extension period. The ipragliflozin dose could be increased to 100 mg if warranted. The primary end-point was change in glycated hemoglobin; secondary end-points were change in insulin dose and bodyweight. Safety outcomes were monitored as treatment-emergent adverse events.

Results: A total of 53 (placebo switched to ipragliflozin) and 108 (ipragliflozin) patients completed the open-label extension (treatment period 2), with 24 and 44 patients, respectively, receiving dose increases. From baseline to end of treatment, the overall mean change (standard deviation [SD]) in glycated hemoglobin was –0.33% (0.72; –3.7 mmol/mol [7.9]), with changes in basal, bolus and total insulin doses of –3.76 IU (SD 3.85 IU), –2.51 IU (SD 7.08 IU) and –6.27 IU (SD 8.16 IU), respectively. No serious drug-related treatment-emergent adverse events or deaths were reported. Treatment-emergent adverse events leading to study discontinuation occurred in zero and three (2.6%) patients in the placebo switched to ipragliflozin and ipragliflozin groups, respectively; all were considered drug-related. There were no cases of severe hypoglycemia or diabetic ketoacidosis, and no safety concerns related to dose increase.

Conclusions: The efficacy and safety of 50 mg, once-daily ipragliflozin in insulin-treated type 1 diabetes mellitus patients were confirmed in this long-term, open-label extension study. No safety concerns were attributed to a dose increase to 100 mg.

INTRODUCTION

Insulin therapy, the current standard of care for patients with type 1 diabetes mellitus, can lead to hypoglycemia and weight gain, representing a challenge for successful disease management[1–3]. Glycated hemoglobin (HbA1c) is used as an index of mean glycemia for monitoring long-term glycemic status in patients with diabetes mellitus[4]. Higher HbA1c levels are associated with an increased risk of developing diabetes-related complications[5,6]. Japanese epidemiological data showed that HbA1c levels tend to be higher in patients with type 1 diabetes (mean: 7.82%) compared with type 2 diabetes (mean 7.03%)[7].

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To address the difficulties in successfully controlling type 1 diabetes, novel therapies to help manage blood glucose without inducing hypoglycemia or weight gain are required to improve type 1 diabetes outcomes.

Sodium–glucose cotransporter 2 (SGLT2) is a sodium-dependent glucose transport protein responsible for the majority of glucose reabsorption in the kidney, and is primarily expressed in the proximal renal tubules[8]. Ipragliflozin, an SGLT2-selective inhibitor, was jointly discovered and developed by Astellas Pharma Inc. and Kotobuki Pharmaceutical Co., Ltd.[9,10], and was first approved in Japan in 2014 for the treatment of type 2 diabetes as the first drug in its class[11]. Ipragliflozin inhibits glucose reabsorption by SGLT2 in the proximal renal tubules, resulting in increased glucose excretion in the urine, thereby reducing blood glucose levels.

The safety and efficacy of ipragliflozin in type 2 diabetes patients has been shown through clinical trials and post-marketing surveys[12–19]. Several studies have shown that ipragliflozin lowers blood glucose levels in an insulin-independent fashion[20,21], and hence is expected to be efficacious in type 1 diabetes, as well as type 2 diabetes.

A 2-week pharmacokinetic/pharmacodynamic study of ipragliflozin in Japanese type 1 diabetes patients with poor glycemic control showed dose-dependent increases in the area under the curve, and maximum plasma concentration in patients treated with ipragliflozin (25, 50 and 100 mg, once-daily doses). A reduced plasma glucose level and greater mean change from baseline for total daily insulin dose were observed in ipragliflozin-treated patients compared with placebo. Ipragliflozin was well tolerated, with mostly mild adverse events (AEs) and no study discontinuations due to treatment-emergent AEs (TEAEs)[22].

The present phase III study was initiated to determine the safety and efficacy of ipragliflozin in patients with type 1 diabetes and inadequate glycemic control with insulin therapy. This study was carried out in two periods: a 24-week, randomized, placebo-controlled period (treatment period 1) and a 28-week open-label extension period (treatment period 2). The overall aims were to determine the superiority of ipragliflozin (50 mg, once-daily) to placebo in terms of change in HbA1c level in treatment period 1, and to assess the safety and efficacy of both long-term (52-week) ipragliflozin treatment and a dose increase to 100 mg once-daily in treatment period 2. Results from treatment period 1 showed a significant reduction in HbA1c, daily insulin dose (basal, bolus and total) and bodyweight in type 1 diabetes patients treated with once-daily 50 mg ipragliflozin compared with placebo, and no safety concerns were observed after 24 weeks of treatment[23].

The present report describes results from the 28-week open-label extension period to assess the long-term (52-week) efficacy and safety of ipragliflozin. Patients in the ipragliflozin group from the double-blind phase continued ipragliflozin, and patients in the placebo group were switched to 50 mg ipragliflozin at the start of the extension period.

METHODS

Patients

Men or women were eligible for the study if they were aged ≥20 years, diagnosed by their attending physician with type 1 diabetes and had received insulin therapy for at least 12 weeks before visit 1 (−6W), with a body mass index of 20.0–35.0 kg/m^2, fasting blood C-peptide level <0.1987 nmol/L (<0.6 ng/mL), and HbA1c (National Glycohemoglobin Standardization Program value) between 7.5% and 11.0% (58–97 mmol/mol) at the time of screening. There were no type 1 diabetes subtype restrictions, and no requirements for antibody testing. Patients were excluded if they had received hypoglycemic agents other than insulin or an alpha-glucosidase inhibitor within 8 weeks before visit 1 (−6W), or had experienced diabetic ketoacidosis (DKA) or major hypoglycemia requiring the assistance of a caregiver within 12 weeks before visit 1 (−6W). Detailed inclusion and exclusion criteria for this study are published in the report describing the double-blind phase (treatment period 1)[23].

Patients were recruited from 36 study centers throughout Japan, and they were allocated by factoring in the study sites for randomization. Those who had completed the 24-week double-blind period continued to the 28-week open-label extension period. All patients provided written informed consent.

Study design and treatments

This article describes the uncontrolled, open-label extension of a multicenter, randomized, placebo-controlled, phase III study in insulin-treated patients with type 1 diabetes and inadequate glycemic control[23]. The study design is shown in Figure S1. Patients taking an alpha-glucosidase inhibitor before entering the study underwent a 4-week washout period. All patients participated in an initial observation period that included a 4-week screening followed by a 2-week placebo run-in, which was immediately followed by treatment period 1 (i.e., the 24-week double-blind phase). Patients with no safety concerns at the end of treatment period 1 entered the 28-week, open-label phase (treatment period 2), in which all patients received 50 mg, once-daily ipragliflozin.

During the study, if a patient felt any hypoglycemic symptoms (such as a sudden strong feeling of hunger and cold sweat), they were instructed to measure their blood glucose levels by themselves as soon as possible. Patients were asked to carry out self-monitoring of blood glucose seven times a day (before breakfast, 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) on any 3 days during the week before each scheduled visit at week 0, 12, 24, 52 and follow up; patients were asked to select 3 days during which significant changes in lifestyle were not expected as far as possible. There was no limitation on how frequently blood glucose testing should be carried out at other times during the study.

The ipragliflozin dose could be increased to 100 mg at week 32 if efficacy was inadequate (HbA1c ≥8.0% at week 28), and no safety concerns were identified up to week 32. If a safety

concern was observed with 100 mg ipragliflozin, the dose could be reduced to 50 mg, but could not be further adjusted after dose reduction. If a dose reduction was required to reduce the risk of hypoglycemia (i.e., self-monitored blood glucose <80 mg/dL [4.44 mmol/L]), a reduction of insulin dose was considered first, and if necessary, reduction of ipragliflozin was then considered. Insulin dose could be adjusted at any time in accordance with the method implemented in the patient's usual care settings, as instructed by their physicians. A 15% reduction in insulin dose was recommended at baseline relative to the patient's dose at screening.

Prohibited concomitant medications included hypoglycemic agents (other than insulin); alpha-glucosidase inhibitors; continuous systemic corticosteroid treatment or immunosuppressants, except for topical application (temporary use was allowed); and treatments for hypoglycemia (except orally administered glucose). Patients requiring hospitalization for the treatment of diabetes or treatment for hypoglycemia other than self-administered oral glucose were withdrawn from the study. Treatment compliance was verified by accounting for the study drug at each patient visit. Further information regarding the study design can be found in the published double-blind phase paper[23].

The present study was carried out in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice, Guidelines of International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, and applicable laws and regulations. The protocol, case report form, written information for patients and consent were approved by the institutional review board at each study site. This study is registered at ClinicalTrials.gov (NCT02897219).

Efficacy outcomes

The primary efficacy outcome was the change in HbA1c from baseline. We assessed both the maintenance of efficacy of long-term (52-week) ipragliflozin treatment and the efficacy of a dose increase to 100 mg in patients with an inadequate response to 50 mg. Insulin dose and bodyweight were analyzed as secondary efficacy outcomes, and change in HbA1c at the end of treatment according to baseline HbA1c was assessed as a subanalysis.

Safety

Safety outcomes included AEs, TEAEs, occurrence of hypoglycemia- and ketone body-related TEAEs, vital signs, general laboratory tests (hematology, blood chemistry including fractional ketone bodies and urinalysis), and 12-lead electrocardiogram. Measurements for ketone body-related parameters were carried out on blood samples drawn after fasting. Hypoglycemia-related AEs included all incidences of blood glucose ≤70 mg/dL (≤3.89 mmol/L), as well as those of symptomatic hypoglycemia (typical symptoms of hypoglycemia, blood glucose not measured) and relative hypoglycemia (typical symptoms of hypoglycemia, blood glucose >70 mg/dL [>3.89 mmol/L]). Hypoglycemia was considered major if the incident required the assistance of a caregiver; all other incidences were considered minor. AEs were coded by System Organ Class and Preferred Term according to the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0.

Statistical analysis

The sample size calculation and rationale are described in the 24-week double-blind study report[23]. The full analysis set consisted of all patients who received at least one dose of ipragliflozin and for whom at least one efficacy variable was measured after drug administration. The safety analysis set included all patients who received at least one dose of ipragliflozin. Demographic data were examined using descriptive statistics. The number and percentage for TEAEs and categorical laboratory data, and descriptive statistics for continuous laboratory data and vital signs were reported for the safety analysis set.

For the end-of-study analyses, baseline was defined as the start of treatment period 1 for patients who received 50 mg ipragliflozin in the double-blind phase, and as week 24 (start of treatment period 2) for patients who received placebo in the double-blind phase. Data were analyzed using SAS® Drug Development software (version 4.5 or higher; SAS Institute Inc., Cary, NC, USA) and SAS® software (version 9.4 or higher).

RESULTS

Patients

In the double-blind phase, 54 out of 60 patients in the placebo group and 112 out of 115 patients in the ipragliflozin group completed treatment period 1, and thus entered the open-label phase (treatment period 2). Of these, 53 and 108, respectively, completed treatment period 2 (Figure S2). The full analysis set and safety analysis set included all patients who had received ipragliflozin by the end of treatment period 2, regardless of whether they completed the study; that is, 54 patients in the placebo switched to ipragliflozin group and 115 in the ipragliflozin group. In the placebo switched to ipragliflozin and ipragliflozin groups, zero and three (2.6%) patients discontinued because of TEAEs during period 2, zero and one (0.9%) patient withdrew consent, and one (1.9%) and zero patient withdrew for other reasons, respectively.

The ipragliflozin dose was maintained at 50 mg in 30 patients in the placebo switched to ipragliflozin group, and in 68 patients in the ipragliflozin group; the dose was increased to 100 mg in 24 patients in the placebo switched to ipragliflozin group, and 44 patients in the ipragliflozin group. One patient in the ipragliflozin group who underwent a dose increase subsequently had a dose reduction back to 50 mg; for purposes of the subgroup analyses, this patient was included in the 100 mg dose increase group.

Baseline characteristics of the patients in the placebo switched to ipragliflozin and ipragliflozin groups were generally comparable (Table 1). In both groups, the majority of patients were receiving multiple daily injections of insulin rather than

Table 1 | Demographics and baseline characteristics (full analysis set)

		Placebo → Ipragliflozin (*n* = 54)	Ipragliflozin (*n* = 115)	By dose increase	
				Maintained at 50 mg (*n* = 68)	Increased to 100 mg (*n* = 44)
Sex	Male	22 (40.7)	54 (47.0)	36 (52.9)	16 (36.4)
	Female	32 (59.3)	61 (53.0)	32 (47.1)	28 (63.6)
Age (years)	Mean (SD)	48.0 ± 12.7	49.7 ± 13.1	50.5 ± 13.6	48.8 ± 12.3
	Range	22–74	22–81	22–78	28–81
	<65	47 (87.0)	96 (83.5)	55 (80.9)	39 (88.6)
	≥65	7 (13.0)	19 (16.5)	13 (19.1)	5 (11.4)
Bodyweight (kg)†	Mean (SD)	64.08 ± 9.11§	66.18 ± 11.49	65.37 ± 10.83	67.46 ± 12.82
	Range	50.6–85.9	47.8–114.2	48.7–95.8	47.8–114.2
BMI (kg/m^2)‡	Mean (SD)	24.16 ± 2.65	24.67 ± 2.95	24.32 ± 2.22	25.34 ± 3.74
	Range	20.1–33.5	20.1–34.5	20.1–30.7	20.6–34.5
	<25	32 (59.3)	69 (60.0)	43 (63.2)	24 (54.5)
	≥25	22 (40.7)	46 (40.0)	25 (36.8)	20 (45.5)
Underwent α-GI washout		3 (5.6)	7 (6.1)	2 (2.9)	5 (11.4)
Route of insulin injection‡	CSII	2 (3.7)	8 (7.0)	6 (8.8)	2 (4.5)
	MDI	52 (96.3)	107 (93.0)	62 (91.2)	42 (95.5)
eGFR (mL/min/1.73 m^2)†	Mean (SD)	88.72 ± 17.49§	93.76 ± 20.92	94.33 ± 22.19	93.28 ± 18.69
	Range	56.2–127.1	54.2–152.7	54.2–152.7	57.8–151.3
	30 to <60	1 (1.9)	3 (2.6)	1 (1.5)	1 (2.3)
	60 to <90	31 (58.5)	48 (41.7)	29 (42.6)	19 (43.2)
	≥90	21 (39.6)	64 (55.7)	38 (55.9)	24 (54.5)
HbA1c (%)†	Mean (SD)	8.52 ± 0.78§	8.68 ± 0.81	8.41 ± 0.67	9.13 ± 0.84
	Range	7.2–10.3	7.2–11.4	7.2–9.9	7.5–11.4
	<8.0	13 (24.5)	21 (18.3)	19 (27.9)	1 (2.3)
	≥8.0	40 (75.5)	94 (81.7)	49 (72.1)	43 (97.7)
HbA1c (mmol/mol)†	Mean (SD)	69.6 ± 8.4§	71.4 ± 9.0	68.4 ± 7.4	76.3 ± 9.4
	Range	55–89	55–101	55–85	58–101
	<64	13 (24.5)	21 (18.3)	19 (27.9)	1 (2.3)
	≥64	40 (75.5)	94 (81.7)	49 (72.1)	43 (97.7)
Fasting plasma glucose (mg/dL)†	Mean (SD)	187.1 ± 88.1§	191.8 ± 69.0	172.5 ± 65.5	219.3 ± 66.8
	Range	40–468§	49–351	49–337	63–351
Fasting plasma glucose (mmol/L)†	Mean (SD)	10.38 ± 4.89§	10.65 ± 3.83	9.57 ± 3.64	12.17 ± 3.72
	Range	2.2–26.0§	2.7–19.5	2.7–18.7	3.5–19.5
Basal insulin dose (IU/day)	Mean (SD)	19.92 ± 10.19§	19.15 ± 9.80	18.75 ± 8.78	19.85 ± 11.52
	Range	5.0–58.0	2.0–74.3	2.0–46.0	8.0–74.3
Bolus insulin dose (IU/day)	Mean (SD)	30.81 ± 16.58§	30.09 ± 15.62	28.54 ± 12.44	32.15 ± 19.57
	Range	9.0–79.0	7.3–102.0	7.3–75.3	10.3–102.0
Total insulin dose (IU/day)	Mean (SD)	50.73 ± 24.56§	49.24 ± 22.58	47.29 ± 17.70	52.00 ± 28.86
	Range	19.8–118.0	17.3–176.3	17.3–105.3	20.3–176.3
	<50	33 (62.3)	72 (62.6)	45 (66.2)	25 (56.8)
	≥50	20 (37.7)	43 (37.4)	23 (33.8)	19 (43.2)
Total insulin dose (IU/kg·day)†	Mean (SD)	0.77 ± 0.30§	0.74 ± 0.28	0.73 ± 0.24	0.75 ± 0.33
	Range	0.3–1.6	0.2–2.2	0.2–1.5	0.3–2.2
	<0.3	0	1 (0.9)	1 (1.5)	0
	≥0.3	53 (100.0)	114 (99.1)	67 (98.5)	44 (100.0)
Reduction of daily dose of insulin preparation, visit 3 (0W)	No	27 (50.0)	62 (53.9)	32 (47.1)	27 (61.4)

Data are shown as *n* (%) unless otherwise indicated. BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; α-GI, alpha-glucosidase inhibitor; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; SD, standard deviation; W, week. †At baseline. ‡2 weeks before start of treatment period 1. §*n* = 53.

continuous subcutaneous insulin infusion. In the ipragliflozin group, the mean (standard deviation [SD]) baseline HbA1c and fasting plasma glucose levels were higher in patients whose dose was increased to 100 mg than in patients whose dose was maintained at 50 mg (Table 1).

The mean duration of study treatment was 199.3 days (SD 19.5 days) in the placebo switched to ipragliflozin group, and 359.9 days (SD 45.4 days) in the ipragliflozin group. The mean treatment compliance for the study was 98.8% (SD 1.9%) and 98.4% (SD 2.2%) in the placebo switched to ipragliflozin and ipragliflozin groups, respectively.

HbA1c

HbA1c levels decreased at week 4 in the ipragliflozin group and at week 28 in the placebo switched to ipragliflozin group (4 weeks after initiation of ipragliflozin treatment); this decrease was maintained in both groups through to week 52 (Figure 1). The mean change in HbA1c from baseline to the end of treatment was −0.33% (SD 0.72%; −3.7 mmol/mol [7.9]). The mean changes in HbA1c in the ipragliflozin group were generally similar among subgroups of patients divided by baseline characteristics, except in patients divided by baseline HbA1c of <8.0% (<64 mmol/mol) versus ≥8.0%: −0.06% (SD 0.44%;

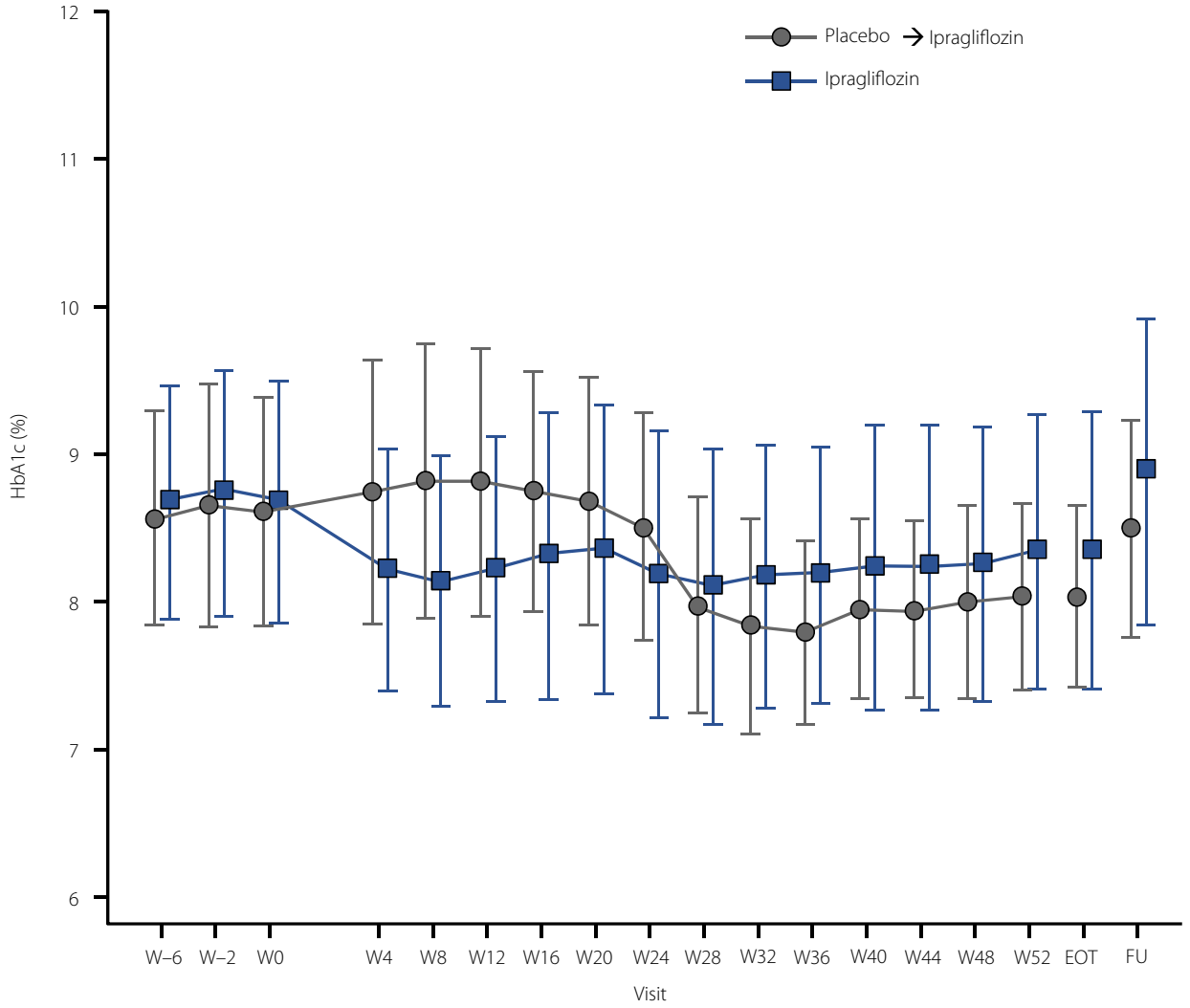

Figure 1 | Change in glycated hemoglobin (HbA1c; %). Data are shown as the mean ± standard deviation in National Glycohemoglobin Standardization Program units. Patients in the placebo switched to ipragliflozin group were switched to ipragliflozin at week 24. EOT, end of treatment; FU, follow up; W, week.

−0.8 mmol/mol [5.0]) versus −0.39% (SD 0.76%; −4.3 mmol/mol [8.3]), respectively.

Differences in baseline HbA1c were identified in patients who underwent a dose increase versus those who did not (excluding dropouts before week 32): mean baseline HbA1c levels were 9.13% (76.3 mmol/mol) in the 100 mg dose group and 8.41% (68.4 mmol/mol) in the 50 mg group. An ipragliflozin dose increase resulted in decreased HbA1c levels. Any decrease, a ≥0.3% (3.3 mmol/mol) decrease or a ≥0.5% (5.5 mmol/mol) decrease were achieved in 20 (46.5%), 16 (37.2%) and five (11.6%) patients, respectively, at 12 weeks after the dose increase; and 23 (52.3%), 13 (29.5%) and eight (18.2%) patients at the end of treatment.

Secondary efficacy outcomes

The basal daily insulin dose decreased until week 16, and the bolus and total daily insulin doses decreased until week 8 in the ipragliflozin group; these decreases were maintained until week 52. A reduction in daily insulin dose from baseline to the end of treatment was observed for basal, bolus and total daily insulin with respective mean changes of −3.76 IU (SD 3.85 IU), −2.51 IU (SD 7.08 IU) and −6.27 IU (SD 8.16 IU). Percentage changes in daily insulin dose are shown in Figure S3.

Mean bodyweight decreased by 3.13 kg from baseline through to the end of treatment in the ipragliflozin group, with a clear reduction at approximately week 12 that was maintained until the end of treatment (Figure S4). Mean changes in bodyweight from baseline to the end of treatment according to ipragliflozin dose increase were −2.95 and −3.43 kg (−4.56% and −5.30%) in the 50 mg maintenance and 100 mg dose increase groups, respectively.

The mean change in fasting blood glucose from the start to end of treatment was −30.3 mg/dL (−1.68 mmol/L) in the ipragliflozin group, and −11.5 and −60.7 mg/dL (−0.64 and −3.36 mmol/L) in the 50 mg maintenance and 100 mg dose increase groups, respectively.

Safety

AEs

TEAEs, drug-related TEAEs and serious TEAEs occurred in 54 (100.0%), 51 (94.4%) and two (3.7%) patients in the placebo switched to ipragliflozin group, respectively. In the ipragliflozin group, the respective incidences were 115 (100.0%), 115 (100.0%) and two (1.7%). There were no serious drug-related TEAEs. TEAEs leading to study discontinuation occurred in zero patients in the placebo switched to ipragliflozin group, and three (2.6%) patients in the ipragliflozin group; these events were considered drug-related. A total of 52 (96.3%) and 115 (100.0%) patients in the placebo switched to ipragliflozin and ipragliflozin groups, respectively, experienced hypoglycemia-related TEAEs, and seven (13.0%) and 20 (17.4%) patients experienced increased ketone body-related TEAEs (Table 2). Genital infections occurred in nine (7.8%) patients in the ipragliflozin group, with genital pruritus having the highest incidence (4.3%); other observed genital infections were genital candidiasis, vaginal infection, vulvovaginal candidiasis and vulvovaginal pruritus, each of which occurred at an incidence of 0.9%. No deaths were reported.

There were no safety concerns attributed to ipragliflozin dose increase. The incidence of TEAEs (in cases/patient-years) was not correlated with the dose of ipragliflozin (Table S1).

TEAEs related to hypoglycemia (including drug-related TEAEs) were observed in all patients in the ipragliflozin group; however, just five patients experienced moderate-severity AEs of this type, all others mild. There were no hypoglycemia-related serious TEAEs or TEAEs leading to discontinuation; timing of onset for hypoglycemia-related TEAEs was highest between weeks 0 and 12 (Table S2). Two TEAEs related to major hypoglycemia (i.e., severe enough to require the assistance of a third person) were reported in the placebo switched to ipragliflozin and ipragliflozin groups (one patient each).

The incidence of TEAEs related to increased ketone bodies was 17.4% in the ipragliflozin group. Those observed in two or more patients included increased blood ketone bodies (14 patients) and ketosis (four patients); there were no cases of DKA. During the 52-week study, four patients (three women) taking ipragliflozin developed ketosis, and all of these patients were receiving multiple daily injections of insulin. Regarding ketone bodies, the mean change from baseline to final drug administration was 247.11 μmol/L (SD 416.59 μmol/L) for total ketone bodies, 57.01 μmol/L (SD 99.34 μmol/L) for acetoacetic acid and 189.95 μmol/L (SD 329.10 μmol/L) for 3-hydroxybutyric acid (Table 3). Changes over time for total serum ketone bodies for individual patients are shown in Figure S5. During the treatment period for patients receiving ipragliflozin, a total of six patients at 10 visits had total ketone body levels >3,000 μmol/L; three patients at three visits experienced both a fasting blood glucose level <200 mg/dL and a total ketone body level >3,000 μmol/L.

DISCUSSION

The present long-term study confirmed the safety and efficacy of ipragliflozin add-on therapy for insulin-treated type 1 diabetes patients. The reductions in HbA1c; basal, bolus and total daily insulin doses; and bodyweight that were observed in patients treated with ipragliflozin during the 24-week double-blind period[23] were maintained throughout the open-label extension (up to 52 weeks of treatment). In patients for whom 50 mg, once-daily ipragliflozin was inadequate, a dose increase to 100 mg/day resulted in a further reduction of HbA1c.

Treatment-emergent adverse events occurred in all patients; however, serious TEAEs occurred in just four patients, and none were treatment-related. Although hypoglycemia-related TEAEs were common, the severity of these events was mild in all but five patients, for whom it was moderate. Seven (13.0%) and 20 (17.4%) patients in the placebo switched to ipragliflozin and ipragliflozin groups, respectively, experienced TEAEs related to ketone body increases. There were no cases

Table 2 | Summary of adverse events (safety analysis set)

	Placebo → Ipragliflozin (*n* = 54)		Ipragliflozin (*n* = 115)	
	n (%)	Events	*n* (%)	Events
TEAEs	54 (100.0)	2,057	115 (100.0)	6,792
Drug-related TEAEs	51 (94.4)	1,657	115 (100.0)	5,909
Serious TEAEs	2 (3.7)	3	2 (1.7)	2
Drug-related serious TEAEs	0	0	0	0
TEAEs resulting in discontinuation	0	0	3 (2.6)	3
Drug-related TEAEs resulting in discontinuation	0	0	3 (2.6)	3
TEAEs related to hypoglycemia	52 (96.3)	1,897	115 (100.0)	6,303
TEAEs related to an increase in ketone bodies	7 (13.0)	9	20 (17.4)	24
TEAEs related to urinary tract infections	7 (13.0)	9	9 (7.8)	10
TEAEs related to genital infections	2 (3.7)	2	9 (7.8)	9
TEAEs related to frequent urination or polyuria	3 (5.6)	4	8 (7.0)	8
TEAEs related to volume depletion	2 (3.7)	2	8 (7.0)	8
TEAEs related to weight loss	3 (5.6)	3	10 (8.7)	11
TEAEs related to renal disorders	0	0	2 (1.7)	2
TEAEs related to bone fractures	1 (1.9)	1	2 (1.7)	2
TEAEs related to malignant tumors	1 (1.9)	1	0	0
TEAEs related to cardiovascular disease	0	0	4 (3.5)	4
TEAEs related to skin and subcutaneous tissue disorders	6 (11.1)	8	14 (12.2)	18

Data are shown as *n* (%) # of events. TEAE, treatment-emergent adverse event.

of severe hypoglycemia or DKA, and no safety concerns attributed to ipragliflozin dose increase.

The reduction in HbA1c from baseline observed in the 24-week double-blind treatment period of −0.47% (−5.1 mmol/mol; adjusted mean difference to placebo, −0.36% [−3.8 mmol/mol]) was maintained through to the end of the extension study (−0.33%; −3.7 mmol/mol)[23].

It is notable that the basal-to-bolus insulin ratio reported at baseline in the present study differed from those reported in similar studies of type 1 diabetes patients treated with other SGLT2 inhibitors[24–26]. In the aforementioned studies, basal and bolus insulin doses were roughly similar, whereas in the present study, the basal daily insulin dose was considerably lower (approximately 2/3 that of the bolus daily dose). This, along with the relatively large reduction in basal insulin dose by the end of the study, might have contributed to the absence of severe hypoglycemia for ipragliflozin-treated patients in the present study.

The insulin dose reduction from baseline to the end of treatment was greater in basal (−20.59%) compared with bolus (−8.44%) insulin in the present study, which is similar to that observed in an 18-week study of type 1 diabetes patients taking canagliflozin[24]. In contrast, a 24-week study in type 1 diabetes patients given sotagliflozin reported a greater decrease in bolus (−12.3%) compared with basal (−9.9%) daily insulin dose[25]. In that study, severe hypoglycemia was reported in 3% of patients in the treatment group. This suggests that dose titration for insulin in patients administered concomitant SGLT2 inhibitors is important not just from a perspective of total dose, but effects of basal versus bolus dose titration should be carefully considered.

The Empagliflozin as Adjunctive to inSulin thErapy (EASE) trials[26] examined the efficacy and safety of empagliflozin in type 1 diabetes patients: 2.5 mg (26-week EASE-3) and 10 or 25 mg (26-week EASE-1 and 52-week EASE-2). Overall, efficacy results were similar to the present study, including

Table 3 | Ketone body-related parameters (ipragliflozin group)

	Timing	Ipragliflozin		
		n	Mean (SD)	Change from baseline (SD)
Total ketone bodies (μmol/L)	Baseline	115	200.78 (212.32)	247.11 (416.59)
	End of treatment		447.89 (433.50)	
Acetoacetic acid (μmol/L)	Baseline	115	56.26 (52.14)	57.01 (99.34)
	End of treatment		113.27 (100.81)	
3-hydroxybutyric acid (μmol/L)	Baseline	115	144.57 (162.54)	189.95 (329.10)
	End of treatment		334.52 (345.30)	

Reference ranges: total ketone bodies, 26.0–122 μmol/L; acetoacetic acid, 13.0–69.0 μmol/L; 3-hydroxybutyric acid, ≤76.0 μmol/L. SD, standard deviation.

significant reductions in HbA1c, bodyweight and total daily insulin dose compared with baseline for all dose groups. Clinical trials in type 1 diabetes patients with other SGLT2 inhibitors[24,25,27,28] (dapagliflozin [24 weeks], canagliflozin [18 weeks] and sotagliflozin [24 weeks]) have also reported similar efficacy results with significant reductions in HbA1c, weight and total daily insulin dose.

Regarding safety, the incidence of severe hypoglycemia in the EASE trials[26] was somewhat higher in the 10 and 25 mg dose groups than in the 2.5 mg and placebo groups, and was higher than that reported in the present study in either treatment period. The canagliflozin trial also reported higher incidences of severe hypoglycemia in canagliflozin-treated versus placebo patients (up to 6.8% in canagliflozin-treated patients vs 1.7% for placebo)[24].

Similar trials[25–28] of other SGLT2 inhibitors reported incidences of DKA, typically correlated with increased study drug dosing. Although the present study reported no cases of DKA, fewer patients were included than in other similar studies. Increases in ketone body-related parameters in patients treated with ipragliflozin that were reported in the 24-week double-blind treatment period[23] were confirmed in the present study. Results from the previous trials and those of the present study suggest that type 1 diabetes patients administered with concomitant SGLT2 inhibitors might need to be carefully monitored for ketone body-related AEs. A recent consensus report has recommended precautions for enhancing the safety of SGLT2 inhibitors in light of the increased risk of DKA for type 1 diabetes patients[29]. Specifically, clinicians should be fully informed of the safe use and risks when prescribing SGLT2 inhibitors for type 1 diabetes, and consider the baseline ketone levels, patient demographic/behavioral factors and potential for euglycemic DKA. Patients should be educated on the causes and symptoms of DKA, and the possibility of euglycemic DKA, counseled on the importance of ketone monitoring and ketosis treatment protocols, and instructed on when to seek medical attention.

The present study reported a high incidence of hypoglycemia-related TEAEs, particularly compared with the incidences observed in clinical trials of ipragliflozin in type 2 diabetes patients[12,13,30]. However, a recent meta-analysis suggested that SGLT2 inhibitor add-on therapy to insulin does not significantly increase the risks of hypoglycemia or severe hypoglycemia in type 1 diabetes patients[31]. It is important to note that although hypoglycemia was a frequent TEAE in type 1 diabetes patients treated with ipragliflozin in combination with insulin, there were just two episodes of major hypoglycemia in the present study, neither of which were ruled as serious.

A limitation of the present study is that patients who experienced major hypoglycemia or DKA 3 months before study enrollment were excluded; inclusion of these patients might have influenced the safety results. The present study did not include an adequate number of cases to determine the impact of insulin injection or the effects of insulin preparations; however, both will be addressed in a comparative study.

We previously reported a statistically significant reduction in HbA1c after 24 weeks of treatment with ipragliflozin versus placebo in treatment period 1. Here, we report that this was maintained to the end of treatment period 2 (week 52). We also found that a dose increase to once-daily 100 mg ipragliflozin was associated with a meaningful improvement in HbA1c among patients for whom once-daily 50 mg ipragliflozin was inadequate. The safety profile of ipragliflozin in type 1 diabetes patients, as shown in treatment period 1, was confirmed in this long-term, open-label extension study.

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DISCLOSURE

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SUPPORTING INFORMATION

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

Figure S1 | Study design.

Figure S2 | Patient disposition.

Figure S3 | Percent change in insulin dose.

Figure S4 | Change in bodyweight.

Figure S5 | Total serum ketone bodies.

Table S1 | Comparison of safety outcomes before and after ipragliflozin dose increase at week 32.

Table S2 | Onset of treatment-emergent adverse events related to hypoglycemia (ipragliflozin group).