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A phase 3 randomized placebo-controlled trial to assess the efficacy and safety of ipragliflozin as an add-on therapy to metformin in Russian patients with inadequately controlled type 2 diabetes mellitus

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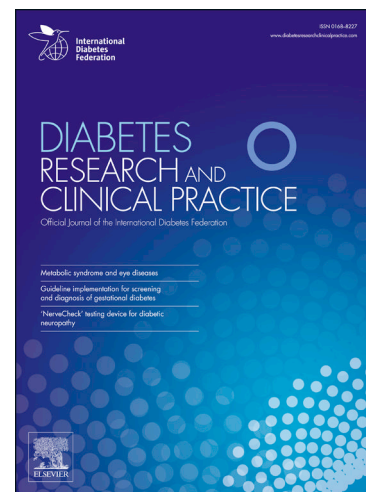
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Full title: A phase 3 randomized placebo-controlled trial to assess the efficacy and safety of ipragliflozin as an add-on therapy to metformin in Russian patients with inadequately controlled type 2 diabetes mellitus

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Abstract

AIM: To assess the efficacy and safety of ipragliflozin as add-on therapy to metformin in Russian patients with type 2 diabetes mellitus.

METHODS: In this double-blind study conducted in 14 centers in Russia, 165 patients were randomized 2:1 to ipragliflozin (50 mg/day) or placebo for 24 weeks while continuing metformin. Patients who had HbA1c ≥7.0% (53 mmol/mol) at Week 12 received open-label ipragliflozin (50 mg/day) in addition to the blinded drug from Week 12–24.

RESULTS: Significant reductions in HbA1c and body weight from baseline to Week 12 in favor of ipragliflozin were observed (adjusted mean difference to placebo: -0.3% (-3 mmol/mol) , P=0.048 and -1.34 kg, P<0.001, respectively). The incidence of AEs was similar in both groups. Uptitration to 100 mg/day ipragliflozin led to a further reduction in body weight (mean change from Week 12: -0.65 kg, P=0.004) and an additional 13% (9/69) of patients achieving HbA1c <7.0% (53 mmol/mol) at Week 24. Incidence of AEs was similar among patients receiving ipragliflozin 50 mg/day (23.7%) and 100 mg/day (24.6%).

CONCLUSION: Ipragliflozin 50 mg/day added to metformin significantly reduced HbA1c and body weight after 12 weeks and showed a safety profile comparable to placebo. Uptitration to 100 mg/day improved clinical outcomes with no additional safety concerns.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a growing concern worldwide, having reached epidemic proportions in many developing and most developed countries [1]. Data from the Russian State Diabetes Registry estimated the prevalence of T2DM in Russia at 2.97%; however, the 2016 NATION study suggests it is much higher at 5.4%, where over half were undiagnosed [2]. Despite efforts to estimate the prevalence of diabetes in Russia [1, 2], the true prevalence of T2DM is likely to be even higher than reported.

Current international treatment guidelines recommend the use of metformin as first-line therapy in patients with T2DM, in conjunction with lifestyle interventions such as diet and exercise [3, 4]. If glucose control remains inadequate, a combination of metformin and one of the following class of antidiabetic agents is recommended: sulfonylureas, dipeptidyl peptidase 4 inhibitors, thiazolidinediones, GLP-1 receptor agonists, or sodium-glucose co-transporter-2 (SGLT2) inhibitors [3, 4]. Among these, SGLT2 inhibitors are the only class of oral antidiabetic agents that improve glycemic control by an insulin-independent mechanism. SGLT2 inhibitors lower blood glucose by reducing glucose reabsorption and increasing urinary excretion of glucose [5]. Given that SGLT2 inhibitors work independently of insulin secretion and action, progressive β-cell failure in T2DM does not attenuate their efficacy and they may therefore be used at any stage of T2DM, including in combination with insulin therapy.

Ipragliflozin is a SGLT2 inhibitor that has been approved for use in the treatment of T2DM in Japan and Korea [6, 7]. Its beneficial effects on glycemic control and body weight have been demonstrated in a number of randomized, double-blind, placebo-controlled trials [8-16]. Since then, a post-marketing long-term study of ipragliflozin has further demonstrated its efficacy and safety in patients with T2DM [17]. While the efficacy and safety of ipragliflozin have been demonstrated in previous phase 3 trials, the majority of these trials were conducted in Asia. Thus, this phase 3, double-blind, randomized, placebo-controlled study aimed to examine the efficacy and safety of ipragliflozin as an add-on therapy to metformin in Russian patients with inadequately controlled T2DM.

2. Materials and methods

This phase 3, double-blind, randomized study was conducted between May 2016 and June 2017 at 14 sites in Russia. The local independent ethics committee at each site reviewed and approved the study protocol and documents used for informed consent prior to study initiation. The study was conducted in accordance with Good Clinical Practice, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, and the Declaration of Helsinki [18]. All patients provided written informed consent before any study-related procedures were performed. This study was registered at ClinicalTrials.gov (identifier NCT02794792).

2.1 Study population

Patients were assessed for study eligibility at the screening visit. Key inclusion criteria included: aged ≥18 years; diagnosed with T2DM for ≥12 weeks; treated with metformin at a stable dose of ≥1500 mg/day for ≥12 weeks; glycated hemoglobin (HbA1c) between 7.5% (58 mmol/mol) and 11.0% (97 mmol/mol) (inclusive); and body mass index (BMI) between 20 to 45 kg/m^2 (inclusive). Key exclusion criteria were: type 1 diabetes mellitus; treated with any medication for glycemic control (except metformin) within 12 weeks; received systemic corticosteroids within 12 weeks; had a stroke, unstable angina, myocardial infarction, any vascular intervention or heart failure within 12 weeks; history of diabetic coma or precoma; history of ketoacidosis or lactic acidosis; and pregnant or lactating. A full list of inclusion and exclusion criteria is available in the supplementary material.

2.2 Study design and treatments

Patients were enrolled by study investigators. Eligible patients entered a 2-week placebo run-in period, during which single-blind placebo was given in addition to metformin; patients' ability to adhere to the treatment regimen and protocol procedures was assessed. This was followed by a 24-week double-blind treatment period (consisting of Period I [Week 0–12] and Period II [Week 12–24]) where patients were randomized (2:1) to ipragliflozin (50 mg/day) or placebo while continuing metformin treatment. A centralized designated interactive web response system (Cenduit, Allschwil, Switzerland) was used to randomize

and assign patients to ipragliflozin or placebo treatment. The randomization was stratified by study center using a block design procedure. At the end of Period I, patients with HbA1c ≥7.0% (53 mmol/mol) and who did not have intolerable adverse events potentially related to ipragliflozin were uptitrated by addition of open-label ipragliflozin (50 mg/day) to their blinded treatment for a further 12 weeks (Period II); patients with HbA1c <7.0% (53 mmol/mol) at the end of Period I continued their double-blind treatment regimen without uptitration in Period II. Only patients that completed the 12-week treatment period in Period I were included in Period II. All patients were followed for a further 4 weeks after the end of treatment.

Metformin tablets were provided by the sponsor from the placebo run-in period until the end of study. Glucometers and test strips used were standardized across study sites and provided to patients for monitoring of blood glucose twice daily (fasting and 2 hours after a meal) on at least 2 days each week until the end of the study. Glucometer readings were recorded in patient diaries and reviewed by the investigator at each visit. The study medications (i.e. placebo and ipragliflozin) were indistinguishable in terms of appearance, taste and aroma. Assignment to study medications was blinded to patients, investigators, clinical staff, and the study sponsor. To maintain blinding, measurements of urinary glucose were not made available to the investigators during the study period. With the exception of the prescribed study medications and metformin, use of any drugs that affect plasma glucose levels was prohibited during the study period. Systemic corticosteroids and changes to diet and exercise were also prohibited until the end of the study.

2.3 Study endpoints

The primary efficacy endpoint was the change in HbA1c from baseline (Week 0) to the end of Period I. Secondary endpoints included the change in fasting plasma glucose (FPG), body weight, and waist circumference during Period I and II, and the change in HbA1c during Period II. Key safety endpoints included the incidence of treatment-emergent adverse events (TEAEs), TEAEs leading to treatment discontinuation, as well as changes in vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate), clinical laboratory variables (lipid profile, hematology, biochemistry, and urinalysis), and 12-lead

electrocardiogram (ECG). All clinical laboratory assessments were conducted in a central laboratory (BARC Global Central Laboratory, Gent, Belgium).

TEAEs were defined as adverse events that were observed after the first administration of study medication to the end of the study. TEAEs of special interest included hypoglycemia, urinary tract infection, and genital infection. Classification of hypoglycemic events follow the definitions from the American Diabetes Association and Endocrine Society workgroup report [19].

2.4 Statistical analyses

It was estimated that a sample size of 156 evaluable patients would provide approximately 90% power to detect a statistically significant difference between placebo and ipragliflozin in HbA1c change from baseline at the end of the first 12-week treatment period, assuming a real treatment mean effect of at least 0.5% (6 mmol/mol) change in HbA1c from baseline, a common standard deviation (SD) of 0.9% (10 mmol/mol), and a 2 sided significance level of α = 0.05. Assuming that approximately 5% of randomized patients may discontinue prior to the week 12 visit, a total of 165 randomized patients would be required for the study. Sample size assumptions were based on the results of two earlier phase 3 studies of ipragliflozin [8, 10].

There were two treatment groups in Period I based on the randomized study medication received: placebo and ipragliflozin. There were four treatment groups in Period II based on the randomized study medication received in Period I and the titration decision made at the start of Period II: placebo/placebo (randomized to placebo, not uptitrated), placebo/ipragliflozin 50 mg (randomized to placebo, uptitrated), ipragliflozin/ipragliflozin 50 mg (randomized to ipragliflozin, not uptitrated), ipragliflozin/ipragliflozin 100 mg (randomized to ipragliflozin, uptitrated).

The full analysis set (FAS) consisted of all patients who were randomized and received at least one dose of the study medication during Period I and had at least one post-baseline efficacy measurement. The safety analysis set (SAF) consisted of all patients who took at least one dose of the randomized study medication during the treatment period.

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Primary and secondary efficacy outcomes were assessed in the FAS and safety outcomes were assessed in the SAF. Missing values at the end of each treatment period were derived using the last observation carried forward method. Study medication compliance was calculated as (number of tablets of study medication taken x 100)/number of tablets that should have been taken since the previous visit. Demographics, baseline characteristics, and safety assessments were summarized by treatment group using descriptive statistics. Continuous variables were reported as means and SD, while categorical data were expressed as n (%) in each treatment group. Changes in primary and secondary efficacy endpoints during Period I (from baseline to Week 12) were compared between treatment groups using analysis of covariance (ANCOVA) with treatment as a fixed effect, center as a random effect, and the respective baseline value as a covariate. For data collected during Period II, mean and 95% confidence intervals (CI) were calculated for change from week 12 (end of Period I/start of Period II) to end of Period II (Week 24) using the analysis of variance (ANOVA) model with treatment group as a fixed effect.

After the planned analyses were completed, a >1% (11 mmol/mol) change in HbA1c was noted during the placebo run-in period in 17 patients (10.4%) in the FAS, suggesting that these patients may not have reached a stable HbA1c by baseline as planned for in the design of the study. To assess the impact that the patients with unstable HbA1c at baseline may have had on the primary efficacy endpoint (HbA1c), a post-hoc analysis was performed in a subgroup of patients in the FAS that excluded patients with >1% (11 mmol/mol) change in HbA1c from screening to baseline. All statistical analyses were performed using the SAS® statistical analysis software (SAS Institute, Cary, NC, USA, version 9.3) and a P value less than 0.05 was considered statistically significant.

3. Results

3.1 Patient disposition and baseline characteristics

Patient flow through the study is presented in Figure 1. Of 268 patients who provided informed consent, 165 patients were randomized to 24 weeks of double-blind treatment (Period I: Week 0-12; Period II: Week 12-24). Six patients discontinued the study prior to the end of Period I; reasons for premature discontinuation are shown in Figure 1. The remaining 159 patients entered Period II of the study. No patients were excluded from uptitration due to safety reasons. The FAS consisted of 164 patients in Period I, and 159 patients in Period II. The SAF in Periods I and II consisted of 165 and 159 patients, respectively.

Patient demographics and baseline characteristics are presented in Table 1. Patients in both the placebo group and ipragliflozin group were predominantly white, aged <65 years, and overweight or obese. Baseline characteristics including duration of diabetes and glycemic parameters (HbA1c and FPG) were generally comparable between both groups (Table 1). The percentage of overweight/obese patients at baseline tended to be higher in the ipragliflozin/ipragliflozin 100 mg group than ipragliflozin/ipragliflozin 50 mg group. Baseline waist circumference, HbA1c levels, and FPG levels also tended to be higher in the ipragliflozin/ipragliflozin 100 mg group than ipragliflozin/ipragliflozin 50 mg group (Table 1).

The mean duration of exposure to study medication in Period I was approximately 82 days and mean compliance rate was approximately 100% in both groups. The mean durations of exposure to study medication (both blinded and open-label treatment) and mean compliance rates in Period II were similar to those in Period I.

3.2 Period I: Week 0–12

Glycemic Outcomes

Figure 2 shows the changes in glycemic variables during Period I. The mean±SD HbA1c levels at baseline were 8.4±0.9% (68±10 mmol/mol) and 8.5±1.0% (69±11 mmol/mol) in the ipragliflozin and placebo groups, respectively. After 12 weeks of treatment, significantly larger reductions in HbA1c were observed with ipragliflozin compared with placebo (Figure

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2A). The mean±SD changes in HbA1c from baseline to the end of Period I were -1.0±0.9% (-11±10 mmol/mol) in the ipragliflozin group and -0.8±1.1% (-9±12 mmol/mol) in the placebo group, with an adjusted mean difference of -0.3% (-3 mmol/mol) (95% CI: -0.5 to 0.0% [-6 to 0 mmol/mol); P=0.048). Notably, a greater adjusted difference was observed in the post-hoc analysis that included a subgroup of patients who had stable HbA1c at baseline (n=147; adjusted mean difference: -0.4% (-4 mmol/mol); 95% CI: -0.6 to -0.1% (-7 to -1 mmol/mol); P=0.007) (Supplementary figure). At the end of Period I, a larger proportion of patients achieved HbA1c <7.0% (53 mmol/mol) with ipragliflozin treatment (34.9%; 95% CI: 26.0 to 44.6%) than with placebo (23.6%; 95% CI: 13.2 to 37.0%).

FPG also decreased to a larger extent in the ipragliflozin group from baseline to the end of Period I (Figure 2B). Mean changes from baseline in FPG were -18.0±32.3 mg/dL for ipragliflozin and -8.0±49.7 mg/dL for placebo, with an adjusted mean difference of -12.3 mg/dL (95% CI: -23.5 to -1.1 mg/dL; P=0.032).

Body weight and waist circumference

Decreases in body weight from baseline to the end of Period I were observed for patients in both treatment groups. This reduction was significantly greater for the ipragliflozin group (mean±SD change: -2.01±2.47 kg) than for the placebo group (mean±SD change: -0.62±2.14 kg). The adjusted mean difference in the changes in body weight was -1.34 kg (95% CI: -2.06 to -0.61 kg; P<0.001). At the end of Period I, a higher proportion of patients had a weight reduction ≥5% in the ipragliflozin group (17.4%; 95% CI: 10.8 to 25.9%) compared to those in the placebo group (5.5%; 95% CI: 1.1 to 15.1%).

The mean change in waist circumference from baseline to the end of Period I tended to be larger for ipragliflozin (-1.7±3.9 cm) than for placebo (-1.1±2.5 cm); however, this difference was not statistically significant (-0.59 cm; 95% CI: -1.65 to 0.47 cm; P=0.272).

Safety outcomes

There were no clinically relevant changes in clinical laboratory variables related to lipid profile, hematology, hepatic function, renal function, or electrolytes from baseline to the end of Period I in either treatment group (data not shown). No notable changes in vital signs

were observed between placebo and ipragliflozin; however, there was a trend towards reduction in standing systolic blood pressure in the ipragliflozin group at the end of Period I (mean change: -1.4 mmHg; 95% CI: -3.5 to 0.7 mmHg vs. 1.1 mmHg; 95% CI: -1.5 to 3.7 mmHg in the placebo group). No major changes in ECG results were observed.

The TEAE profile of ipragliflozin was not markedly different from that of placebo (Table 2). The incidence of TEAEs leading to treatment withdrawal was low in both groups (both 1.8%). No drug-related serious TEAEs were observed. The incidences of TEAEs of special interest were generally comparable between treatment groups: hypoglycemia (ipragliflozin: 11.8% [13/110]; placebo: 10.9% [6/55]), symptomatic urinary tract infection (ipragliflozin: 0.0% [0/110]; placebo: 1.8% [1/55]), and genital infection (ipragliflozin: 0.9% [1/110]; placebo: 0.0% [0/55]). All of the hypoglycemic events observed were mild and most were asymptomatic (ipragliflozin: 8.2% [9/110]; placebo: 7.3% [4/55]).

3.3 Period II: Week 12–24

At week 12, 38 patients on placebo and 69 patients on ipragliflozin were uptitrated by the addition of open-label ipragliflozin 50 mg/day to their blinded treatment (Figure 1); the other patients continued on their blinded treatment without uptitration in Period II. Study outcomes of patients in the ipragliflozin/ipragliflozin 50 mg group and the ipragliflozin/ipragliflozin 100 mg group are detailed below.

Glycemic Outcomes

At the start of Period II, patients in the ipragliflozin group who remained on 50 mg/day of ipragliflozin (ipragliflozin/ipragliflozin 50 mg group) had mean±SD HbA1c and FPG levels of 6.5±0.4% (48±4 mmol/mol) and 131.1±22.4 mg/dL, respectively; both HbA1c and FPG levels increased slightly in this group of patients during Period II of the study, however, the increases were not statistically significant (Table 3). For ipragliflozin-treated patients with HbA1c ≥7.0% (53 mmol/mol) at the end of Period I (ipragliflozin/ipragliflozin 100 mg group), uptitration to 100 mg/day ipragliflozin led to an additional 13% (9/69) of patients achieving HbA1c <7% (53 mmol/mol) at the end of Period II; mean HbA1c and FPG levels remained stable in this group of patients during Period II (Table 3).

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Body weight and waist circumference

In ipragliflozin-treated patients who remained on 50 mg/day of ipragliflozin, mean waist circumference decreased significantly from Week 12 to the end of Period II (mean change from Week 12: -1.28 cm, 95% CI: -2.07 to -0.48 cm, P=0.002) (Table 3). There was also a tendency towards reduction in mean body weight; however, this was not statistically significant (Table 3). For patients who were uptitrated to ipragliflozin 100 mg/day, significant reductions were observed from Week 12 to the end of Period II for mean body weight (mean change from Week 12: -0.65 kg, 95% CI: -1.08 to -0.21 kg, P=0.004) and waist circumference (mean change from Week 12: -0.93 cm, 95% CI: -1.52 to -0.34 cm, P=0.002) (Table 3).

Safety outcomes

There were no clinically relevant changes in clinical laboratory variables related to lipid profile, hematology, hepatic function, renal function, and electrolytes from Week 12 to the end of Period II in any treatment group (data not shown). Sitting systolic blood pressure improved from Week 12 to the end of Period II in patients uptitrated to 100 mg ipragliflozin (mean change from week 12: -3.1 mmHg; 95% CI: -5.6 to -0.7 mmHg). No other notable changes in vital signs or ECG results were observed.

The incidence of TEAEs and drug-related TEAEs from the start of Period II to the end of the study was similar between ipragliflozin-treated patients who were uptitrated to 100 mg/day ipragliflozin and those who remained on 50 mg/day (24.6% [17/69] vs 23.7% [9/38]) (Table 2). No serious drug-related TEAEs were reported. One patient who was uptitrated to 100 mg/day ipragliflozin died during the follow-up period (after end of treatment) due to acute myocardial insufficiency; this death was considered to be unrelated to the study medication. The incidence of hypoglycemia was numerically lower in ipragliflozin-treated patients who were uptitrated to ipragliflozin 100 mg/day than those who remained on 50 mg/day (5.8% [4/69] vs 10.5% [4/38]); there were no reports of symptomatic urinary tract infection or genital infection in either group during Period II.

4. Discussion

This is the first clinical study of ipragliflozin in Russian patients with T2DM. Consistent with the findings of previous trials in Asian patients, addition of ipragliflozin 50 mg/day significantly improved glycemic control in terms of HbA1c and FPG, and resulted in body weight loss in Russian patients who had failed to achieve glycemic control with metformin alone. Uptitration of ipragliflozin from 50 mg/day to 100 mg/day in patients with a suboptimal response after 12 weeks led to more patients achieving glycemic control and further reductions in body weight and waist circumference at 24 weeks. Both 50 mg/day and 100 mg/day of ipragliflozin were well tolerated and no previously unreported safety concerns were observed.

The HbA1c-lowering effect of ipragliflozin from baseline was similar in the present study compared with other ipragliflozin add-on to metformin trials conducted in Asia (-1.0% [-11 mmol/mol] vs -0.9% [10 mmol/mol] [8, 10]). However, owing to the large response in the placebo group in this study, the difference between ipragliflozin and placebo was modest compared with previous studies (-0.3% [-3 mmol/mol] vs -1.3% [-14 mmol/mol] [8] and -0.5% [-6 mmol/mol] [10]). During the placebo run-in period (between screening and baseline) where patients received placebo while continuing metformin, we observed unexpectedly large changes in HbA1c in some patients, suggesting that they may not have reached a stable HbA1c by baseline as planned for in the study. Indeed, almost a quarter of patients in the placebo group did not require uptitration in Period II of the study. A post-hoc analysis which excluded patients with >1% (11 mmol/mol) change in HbA1c from screening to baseline demonstrated a greater adjusted mean difference in change in HbA1c (-0.4%) (- 4 mmol/mol) that is more consistent with those reported in previous trials. Even so, only the most striking outliers were excluded in the post-hoc analysis. Further identification and exclusion of patients who may have had similar issues but had less extensive changes in HbA1c during the placebo run-in period will likely make the treatment effects of ipragliflozin more apparent.

As clinical trial participation has been shown to significantly increase adherence to both trial-related and non trial-related treatments [20], the unexpectedly large decrease in

HbA1c may be associated with improved compliance with metformin and diet/exercise during the study. Furthermore, treatment compliance may also have been supported by more frequent patient contacts and regular self-monitoring of blood glucose after the start of the study, both of which play important roles in promoting effective diabetes management.

Urinary glucose excretion caused by SGLT2 inhibition will lead to a loss of calories [21]; thus, it would be reasonable to expect some benefit in terms of body weight with ipragliflozin treatment. Studies of ipragliflozin, including ours, have consistently shown weight loss of approximately 2 to 3 kg after 24 weeks [8, 10]. Body composition studies have shown that initial weight loss is mainly due to loss of body fluids, while subsequent weight loss primarily results from reduced body fat [22-24]. These favorable effects on body weight and composition make ipragliflozin a valuable option for patients who are overweight, or for whom additional weight gain often caused by other antidiabetic agents (such as sulfonylurea, thiazolidinediones, and insulin) should be avoided [25-27].

The blood pressure-lowering effects of SGLT2 inhibitors have been reported in several studies [9, 10, 28, 29]. In this study, we also observed a reduction in systolic blood pressure after 12 weeks of treatment with ipragliflozin. Some have suggested that the blood pressure-lowering effects of SGLT2 inhibitors may be related to its osmotic diuretic effect and/or weight loss effect [30]. Although the exact mechanism is not yet completely understood, the favorable effects on blood pressure and body weight appear to be a class-effect of SGLT2 inhibitors and may potentially offer cardiovascular benefits for patients with T2DM.

In the present study, ipragliflozin was well-tolerated and showed an overall safety profile similar to placebo. The observed safety profile is consistent with those reported in previous ipragliflozin studies which included over 2000 ipragliflozin-treated patients in total [8-15, 31, 32]. Very few patients discontinued treatment as a result of a TEAE in the present study. Importantly, incidences of hypoglycemia were similar between patients receiving ipragliflozin and those receiving placebo. This is expected as the insulin-independent mode of action of SGLT2 inhibitors should not lead to an increased risk of hypoglycemia, as

confirmed in a systematic review of SGLT2 inhibitors [33]. Given its mechanism, however, increased risks of genital infection may be expected; however the incidence of such events is usually relatively low as observed in our study as well as previous phase III studies of ipragliflozin [8, 10]. Moreover, clinical experience with SGLT2 inhibitors across investigational studies have shown that these events can be effectively managed without stopping SGLT2 inhibitor treatment as most infections are usually mild and respond to standard treatment [5, 34-36].

A key element in the design of this study that differs from previous ipragliflozin trials was the uptitration of patients who had not achieved an adequate level of glycemic control after 12 weeks of treatment with the double-blind study medication. This avoids prolonged undertreatment of patients and mimics real-world management where patients with inadequately controlled T2DM can be uptitrated. A consequence of this design, however, was that sample sizes varied widely between treatment groups in Period II, with the placebo/placebo treatment group being especially small in comparison. The selection process for uptitration does not allow direct comparisons of outcomes between treatment groups in Period II as entry into these groups was not subject to randomization; however, it offers the opportunity to examine the effects of increasing the dose of ipragliflozin from 50 mg/day to 100 mg/day in patients with suboptimal response. Interestingly, even though mean HbA1c remained unchanged following uptitration, further improvements in body weight and waist circumference were observed and an additional 13% of patients achieved HbA1c <7% (53 mmol/mol). Additionally, uptitration to 100 mg/day did not result in increased hypoglycemia, genital infection, or urinary tract infections. This suggests that increasing the dose of ipragliflozin to 100 mg/day may be clinically beneficial for a proportion of T2DM patients with insufficient efficacy at a dose of 50 mg/day.

Given the study design and patient population, we believe that the study's findings may be generalizable and applicable to the T2DM population in Russia. No new safety findings related to ipragliflozin were observed and the safety profile was comparable with the well-established safety profile for SGLT2 inhibitors including ipragliflozin.

In conclusion, ipragliflozin 50 mg/day added to metformin treatment improved glycemic control and reduced body weight in Russian patients with T2DM who were inadequately controlled with metformin alone. These findings support those of earlier studies. In patients with inadequate glycemic control when receiving ipragliflozin 50 mg/day, uptitration to 100 mg/day improved clinical outcomes with no additional safety concerns. Taken together, our results demonstrate that ipragliflozin 50 mg/day and 100 mg/day in combination with metformin is effective and well-tolerated in Russian patients with T2DM.

Conflicts of interest

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Tables

Table 1. Patient demographics and baseline characteristics (safety analysis set)

Characteristic	Period I treatment groups		Period II treatment groups			
	Placebo n = 55	Ipragliflozin n = 110	Placebo/ Placebo n = 14	Placebo/ Ipragliflozin 50 mg n = 38	Ipragliflozin/ Ipragliflozin 50 mg n = 38	Ipragliflozin/ Ipragliflozin 100 mg n = 69
Sex						
Male	22 (40.0)	48 (43.6)	8 (57.1)	13 (34.2)	23 (60.5)	25 (36.2)
Female	33 (60.0)	62 (56.4)	6 (42.9)	25 (65.8)	15 (39.5)	44 (63.8)
Race						
White	55 (100.0)	108 (98.2)	14 (100.0)	38 (100.0)	37 (97.4)	68 (98.6)
Asian	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)	1 (2.6)	1 (1.4)
Age, years	58.0 ± 9.5	58.9 ± 9.3	54.4 ± 10.9	59.5 ± 8.9	58.7 ± 9.9	58.9 ± 9.1
Age <65 years	41 (74.5)	80 (72.7)	12 (85.7)	26 (68.4)	26 (68.4)	52 (75.4)
Height, cm	167.1 ± 8.8	168.1 ± 9.6	171.2 ± 12.4	165.8 ± 6.7	169.1 ± 9.7	168.0 ± 9.4
Weight, kg	89.54 ± 15.60	92.74 ± 16.24	96.26 ± 14.40	87.40 ± 15.97	92.41 ± 14.53	93.46 ± 17.30
BMI, kg/m^2	31.95 ± 4.18	32.80 ± 4.76				
<18.5 (underweight)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
18.5–24.9 (normal)	1 (1.8)	4 (3.6)	0 (0.0)	1 (2.6)	3 (7.9)	1 (1.4)
25–29.9 (overweight)	19 (34.5)	30 (27.3)	3 (21.4)	16 (42.1)	9 (23.7)	20 (29.0)
>30 (obese)	35 (63.6)	76 (69.1)	11 (78.6)	21 (55.3)	26 (68.4)	48 (69.6)
Waist circumference, cm	107.21 ± 12.30	108.46 ± 11.98	111.93 ± 10.41	106.16 ± 12.92	106.78 ± 12.93	109.50 ± 11.41
Duration of Type 2 Diabetes Mellitus, months	78.7 ± 55.9	79.8 ± 62.6	69.7 ± 63.4	82.1 ± 55.5	73.3 ± 71.1	83.5 ± 58.9
HbA1c, %	8.46 ± 0.96	8.39 ± 0.93	8.12 ± 1.20	8.59 ± 0.88	7.89 ± 0.75	8.66 ± 0.92
FPG, mg/dL	175.7 ± 43.2	170.9 ± 40.5	146.9 ± 36.2	185.1 ± 41.2	151.6 ± 30.2	178.8 ± 39.8

Values are presented as number (%) or mean ± standard deviation.

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin

Table 2. Treatment-emergent adverse events during Period I (Week 0 to 12) and during Period II to end of study (Week 12 to 24 + 4 Weeks Follow-up) (safety analysis set)

Variable	Period I		Period II to end of study			
	Placebo n = 55	Ipragliflozin n = 110	Placebo/ Placebo n = 14	Placebo/ Ipragliflozin 50 mg n = 38	Ipragliflozin/ Ipragliflozin 50 mg n = 38	Ipragliflozin/ Ipragliflozin 100 mg n = 69
TEAEs	19 (34.5)	32 (29.1)	5 (35.7)	14 (36.8)	9 (23.7)	17 (24.6)
TEAEs by severity[a]						
Mild	13 (23.6)	26 (23.6)	4 (28.6)	9 (23.7)	8 (21.1)	13 (18.8)
Moderate	6 (10.9)	6 (5.5)	1 (7.1)	5 (13.2)	1 (2.6)	3 (4.3)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Serious TEAEs	0 (0.0)	2 (1.8)	1 (7.1)	1 (2.6)	1 (2.6)	3 (4.3)
TEAEs leading to withdrawal of treatment	1 (1.8)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Drug-related TEAEs	4 (7.3)	12 (10.9)	2 (14.3)	2 (5.3)	1 (2.6)	6 (8.7)
Drug-related TEAEs by severity[a]						
Mild	4 (7.3)	11 (10.0)	2 (14.3)	2 (5.3)	1 (2.6)	5 (7.2)
Moderate	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious drug-related TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Drug-related TEAEs leading to withdrawal of treatment	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Drug-related TEAEs leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAEs of special interest						
Hypoglycemia	6 (10.9)	13 (11.8)	2 (14.3)	2 (5.3)	4 (10.5)	4 (5.8)
Symptomatic urinary tract infection	1 (1.8)	0 (0.0)	0 (0.0)	2 (5.3)	0 (0.0)	0 (0.0)
Genital infection	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Values are presented as number (%).
Placebo/placebo: randomized to placebo, not uptitrated; placebo/ipragliflozin 50 mg: randomized to placebo, uptitrated; ipragliflozin/ipragliflozin 50 mg: randomized to ipragliflozin, not uptitrated; ipragliflozin/ipragliflozin 100 mg: randomized to ipragliflozin, uptitrated.

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TEAEs, treatment-emergent adverse events.

[a]The most severe TEAE was counted if the patient presented with two or more TEAEs with varying severity.

Table 3. Changes in efficacy variables from start to end of Period II (Week 12 to 24) (full analysis set)

	Placebo/ Placebo n = 14	Placebo/ Ipragliflozin 50 mg n = 38	Ipragliflozin/ Ipragliflozin 50 mg n = 38	Ipragliflozin/ Ipragliflozin 100 mg n = 69
HbA1c, %				
Mean at Week 12 (SD)	6.41 (0.53)	8.11 (0.85)	6.49 (0.37)	7.83 (0.68)
Mean at Week 24 (SD)	6.31 (0.55)	7.71 (0.88)	6.66 (0.45)	7.83 (0.85)
Mean change from Week 12	-0.10	-0.40	0.16	0.00
(95% CI)*	(-0.38, 0.18)	(-0.57, -0.23)	(-0.01, 0.33)	(-0.13, 0.12)
P value*	0.475	<0.001	0.06	0.982
FPG, mg/dL				
Mean at Week 12 (SD)	121.6 (24.0)	181.3 (45.1)	131.1 (22.4)	163.2 (35.0)
Mean at Week 24 (SD)	129.2 (17.9)	163.6 (32.1)	133.9 (21.0)	161.2 (36.9)
Mean change from Week 12	7.6	-17.7	2.8	-2.0
(95% CI)*	(-8.6, 23.9)	(-27.6, -7.8)	(-7.0, 12.7)	(-9.3, 5.3)
P value*	0.355	<0.001	0.57	0.588
Body weight, kg				
Mean at Week 12 (SD)	94.96 (13.79)	87.06 (15.25)	89.87 (14.22)	91.72 (17.68)
Mean at Week 24 (SD)	94.32 (13.89)	86.00 (15.03)	89.38 (14.85)	91.08 (18.01)
Mean change from Week 12	-0.64	-1.06	-0.48	-0.65
(95% CI)*	(-1.60, 0.33)	(-1.65, -0.48)	(-1.07, 0.10)	(-1.08, -0.21)
P value*	0.195	<0.001	0.107	0.004
Waist circumference, cm				
Mean at Week 12 (SD)	109.6 (9.9)	105.5 (13.5)	104.2 (12.2)	108.2 (12.1)
Mean at Week 24 (SD)	109.1 (10.6)	104.8 (13.2)	102.9 (12.0)	107.2 (12.2)
Mean change from Week 12	-0.50	-0.72	-1.28	-0.93
(95% CI)*	(-1.81, 0.81)	(-1.52, 0.08)	(-2.07, -0.48)	(-1.52, -0.34)
P value*	0.453	0.076	0.002	0.002

*ANOVA model with treatment as fixed effect.
Placebo/placebo: randomized to placebo, not uptitrated; placebo/ipragliflozin 50 mg: randomized to placebo, uptitrated; ipragliflozin/ipragliflozin 50 mg: randomized to ipragliflozin, not uptitrated; ipragliflozin/ipragliflozin 100 mg: randomized to ipragliflozin, uptitrated.
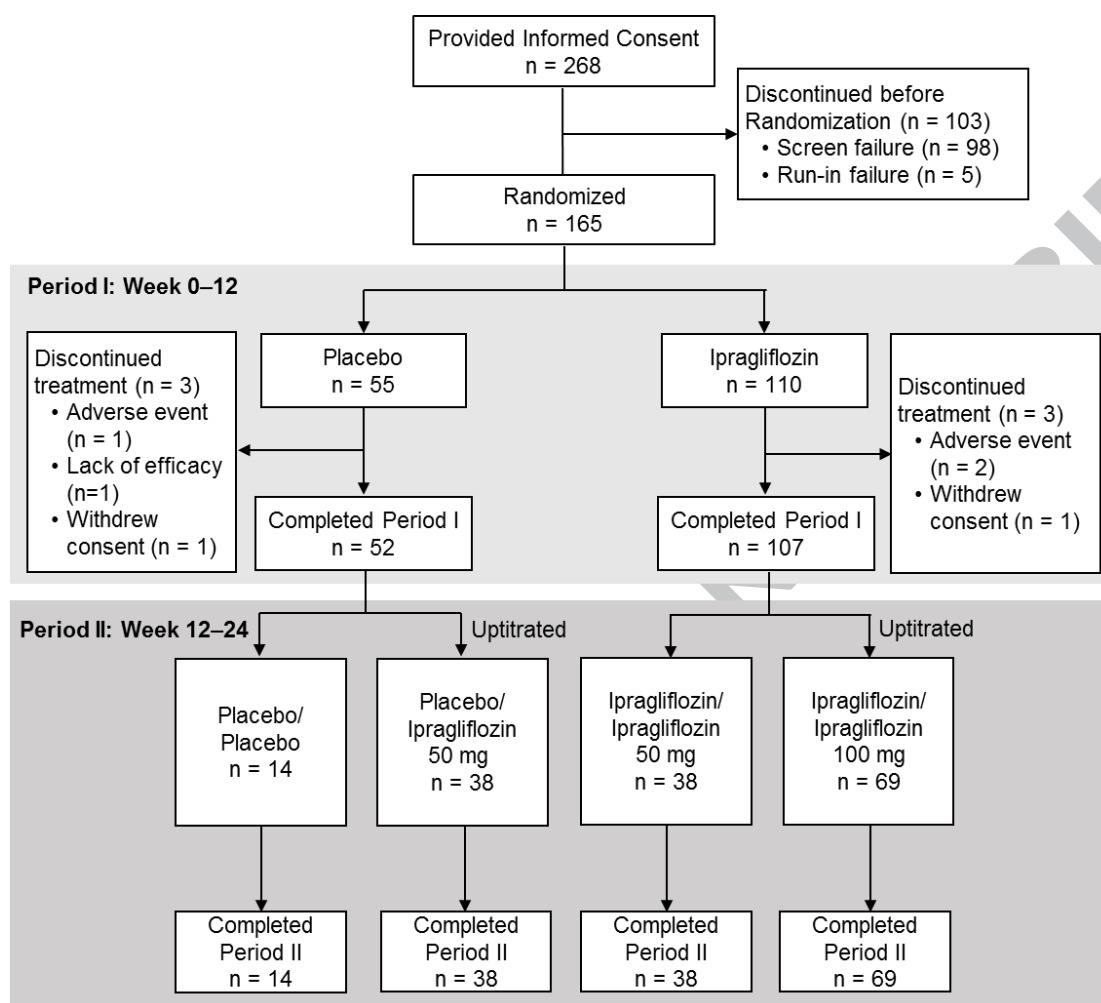FPG, fasting plasma glucose; HbA1c, glycated hemoglobin

Figures

Figure 1. Patient flow through the study. Patients entered a 2-week single-blind placebo run-in period. Eligible patients were randomized to receive double-blind randomized study medication (placebo or ipragliflozin 50 mg/day) for 24 weeks. At the end of Period I (Week 0-12), patients with HbA1c ≥7.0% and who did not have intolerable adverse events potentially related to ipragliflozin were uptitrated by addition of open-label ipragliflozin 50 mg/day to their blinded treatment for a further 12 weeks (Period II: Week 12-24). All patients were followed for a further 4 weeks after the end of treatment. Placebo/placebo: randomized to placebo, not uptitrated; placebo/ipragliflozin 50 mg: randomized to placebo, uptitrated; ipragliflozin/ipragliflozin 50 mg: randomized to ipragliflozin, not uptitrated; ipragliflozin/ipragliflozin 100 mg: randomized to ipragliflozin, uptitrated.
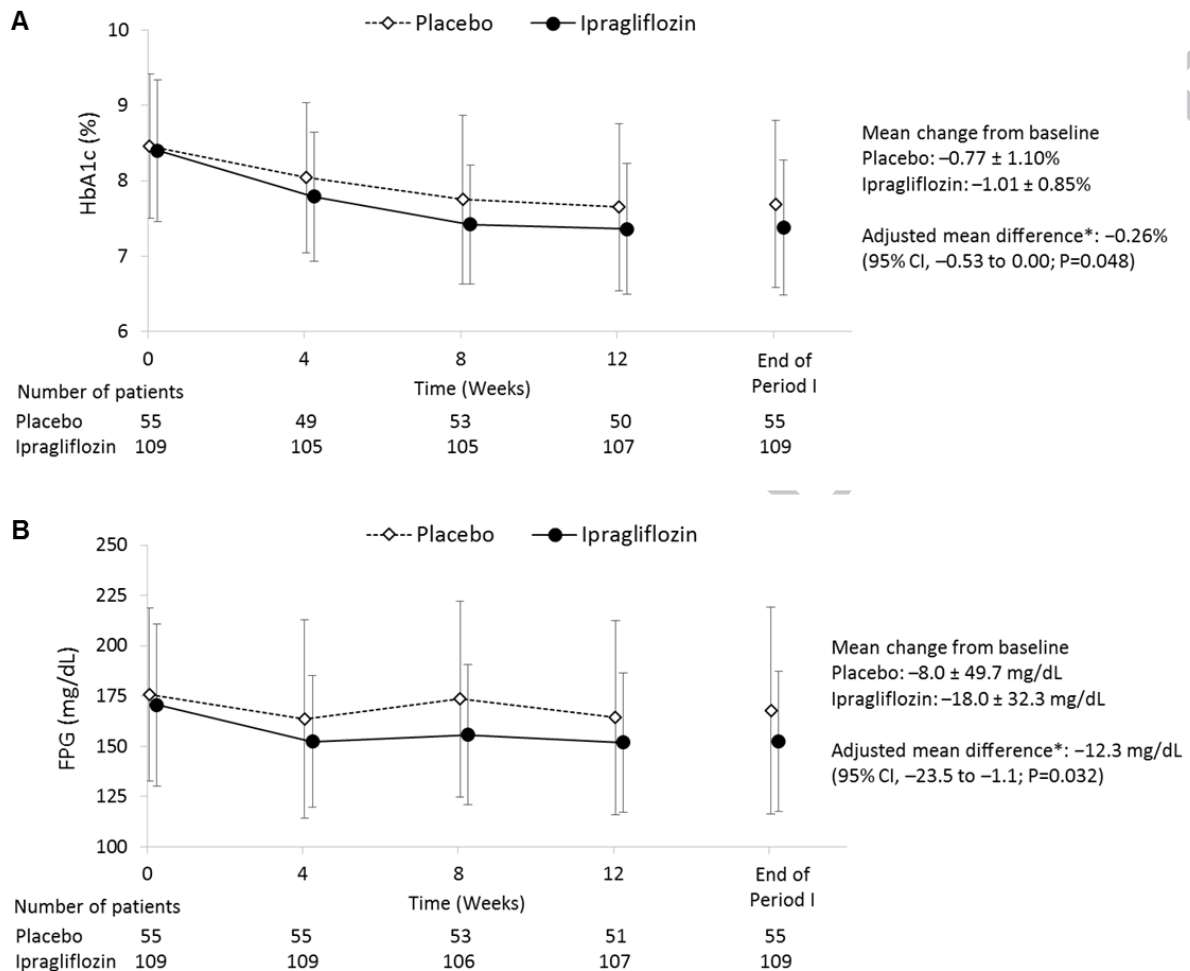
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A

Mean change from baseline
Placebo: −0.77 ± 1.10%
Ipragliflozin: −1.01 ± 0.85%

Adjusted mean difference*: −0.26%
(95% CI, −0.53 to 0.00; P=0.048)

B

Mean change from baseline
Placebo: −8.0 ± 49.7 mg/dL
Ipragliflozin: −18.0 ± 32.3 mg/dL

Adjusted mean difference*: −12.3 mg/dL
(95% CI, −23.5 to −1.1; P=0.032)

Figure 2. Time-courses of (A) glycated hemoglobin (HbA1c) and (B) fasting plasma glucose (FPG) measurements during Period I. Values are mean ± standard deviation. CI, confidence interval. *ANCOVA model including treatment as fixed effect, center as random effect and corresponding baseline value as a covariate.

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