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ORIGINAL RESEARCH

Safety of Ipragliflozin in Patients with Type 2 Diabetes Mellitus: Pooled Analysis of Phase II/III/IV Clinical Trials

Atsunori Kashiwagi · Marina V. Shestakova · Yuichiro Ito · Masahiro Noguchi · Wim Wilpshaar · Satoshi Yoshida · John P. H. Wilding

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ABSTRACT

Introduction: Ipragliflozin is a selective sodium-glucose cotransporter 2 (SGLT2) inhibitor approved for the treatment of type 2 diabetes mellitus (T2DM). The objective of this pooled analysis was to characterise the safety profile of ipragliflozin based on safety data from published randomised controlled trials.

Methods: Safety data from 12 randomised, phase II/III/IV placebo-controlled, parallel group, comparative studies of ipragliflozin in patients with T2DM were pooled. Treatment-emergent adverse events (TEAEs) were analysed for patients who had received at least one dose of ipragliflozin 50 mg (n = 1209) or placebo (n = 796) in studies lasting for up to 24 weeks. TEAEs of special interest and serious adverse events (SAEs) were assessed, as well as abnormal laboratory test and vital sign measurements.

Results: The overall incidences of TEAEs and SAEs between the ipragliflozin and placebo groups were similar, 63.8% vs 59.3% and 2.5% vs 3.3%, respectively. The incidence of TEAEs leading to permanent discontinuation was lower for ipragliflozin (3.6%) than placebo (6.5%). The incidences of TEAEs of special interest including those related to urinary tract infection, cardiovascular events, renal disorder, fracture, malignant tumours and hypoglycaemia were also similar between the groups. Genital infections were more frequent with ipragliflozin (2.4%) than placebo (0.6%), as were pollakiuria/polyuria (6.0% vs 2.0%), volume depletion (4.9% vs 1.8%) and skin/subcutaneous tissue disorders (7.7% vs 4.4%). There were no reported cases of diabetic ketoacidosis, fractures, lower-limb amputation or Fournier's gangrene in ipragliflozin-treated patients across the 12 studies.

Conclusion: In randomised, placebo-controlled trials of patients with T2DM, ipragliflozin was

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A. Kashiwagi (✉)
Kusatsu General Hospital, Kusatsu, Shiga, Japan
e-mail: kashiwagi@kusatsu-gh.or.jp

M. V. Shestakova
Endocrinology Research Centre, Diabetes Institute, Moscow, Russia

Y. Ito · M. Noguchi · S. Yoshida
Astellas Pharma Inc., Tokyo, Japan

W. Wilpshaar
Astellas Pharma Europe B.V., Leiden, The Netherlands

J. P. H. Wilding
Obesity and Endocrinology Research, Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, UK

well tolerated, with a similar overall incidence of TEAEs to placebo. No new safety signals were observed.
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INTRODUCTION

In patients with type 2 diabetes mellitus (T2DM), increased reabsorption of glucose from glomerular filtrate into the circulation is one of the key contributors to elevated blood glucose [1]. Glucose reabsorption is mediated primarily by sodium-glucose cotransporter 2 (SGLT2) of renal tubular cells, and patients with T2DM show enhanced levels of expression of the SGLT2 protein compared with healthy individuals [2].

Pharmacological SGLT2 inhibitors have been developed to lower blood glucose levels in T2DM by blocking its reabsorption and promoting urinary glucose excretion [3, 4]. In addition to improved glycaemic control [5–16], SGLT2 inhibitors provide important clinical benefits for patients with T2DM. Unlike most other anti-hyperglycaemic agents, SGLT2 inhibitors promote weight loss [15, 17], lower blood pressure [18–21] and exert beneficial effects on other cardiometabolic risk factors, except for low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol [22]. Indeed, patients with T2DM at high risk for cardiovascular (CV) events have been shown to have a lower incidence of CV outcomes and death after treatment with SGLT2 inhibitors [23–27]. Furthermore, the insulin-independent mechanism means that the risk of hypoglycaemia is low and their action is not affected by progressive β-cell failure [1, 4]. Thus, SGLT2 inhibitors can be used at any stage of T2DM management, and may also benefit patients with type 1 diabetes mellitus (T1DM) who have inadequate glycaemic control on insulin alone [28–31].

Overall, SGLT2 inhibitors are well-tolerated drugs, but some treatment-emergent adverse events (TEAEs) of special interest have been reported in clinical and post-marketing studies, including urinary tract infection (UTI), genital infection, volume depletion, ketoacidosis [32–34] and some cancers [32, 35, 36]. More recently, reports of increased risk of lower limb amputation [24], fractures [37], Fournier's gangrene [38] and skin and subcutaneous tissue disorders [39–42] have emerged.

Ipragliflozin is an SGLT2 inhibitor which is indicated for the treatment of T1DM, in combination with insulin, and T2DM, either as monotherapy or in combination with other anti-hyperglycaemic agents. It was the first SGLT2 inhibitor to be approved for T2DM in Japan (in 2014 [43]), and has since been approved in Korea and Russia. Individual studies and post-marketing surveillance data suggest that ipragliflozin is well tolerated [5–10, 18, 44–46]. However, safety data from single studies are limited by patient selection and population size, and surveillance data are limited by the lack of a comparator group. The current analysis aims to further establish the safety profile of ipragliflozin in patients with T2DM by analysing data from a large pool of comparative studies.

METHODS

Study Design

Data were pooled from 12 placebo-controlled, parallel group, comparative studies [5–16], of 12, 16 or 24 weeks' duration (Table 1), in which adult patients with T2DM were randomised to treatment with ipragliflozin 50 mg or placebo once daily. Seven of the studies were conducted in Japan, one in Korea, one in Korea and Taiwan, one in Russia and two were global studies (Table 1). In five studies, ipragliflozin treatment was extended open-label up to 52 weeks, while placebo treatment was administered up to a maximum of 24 weeks. As such, the

Table 1 Summary of phase II/III/IV comparative clinical studies included in the pooled safety analysis

Study description Study location [ClinicalTrials.gov identifier]	Design	Dosing regimen	Duration (weeks)
Monotherapy			
Phase II dose-finding [5] Global [NCT01071850]	Randomised, double-blind, placebo- and active-controlled, parallel group dose-finding	Ipragliflozin 12.5, 50, 150, 300 mg QD or placebo or metformin 1000 mg BID for 2 weeks, 1500 mg thereafter	12
Phase II dose-finding [6] Japan [NCT00621868]	Randomised, double-blind, placebo-controlled, parallel group	Ipragliflozin 12.5, 25, 50 or 100 mg QD or placebo	12
Phase III [9] Japan [NCT01057628]	Randomised, double-blind, placebo-controlled, parallel group	Ipragliflozin 50 mg QD or placebo	16
Combination therapy			
Phase IIb metformin combination dose-finding [10] Global [NCT01117584]	Randomised, double-blind, placebo-controlled, parallel group dose-finding	Ipragliflozin 12.5, 50, 150, 300 mg QD or placebo with metformin ≥ 1500 mg QD as prescribed	12
Phase III metformin combination [11] Japan [NCT01135433]	Randomised, double-blind, placebo-controlled, parallel group + open-label uncontrolled[a]	Period 1: Ipragliflozin 50 mg QD or placebo with metformin Period 2: Ipragliflozin 50 mg[b] QD with metformin	24 + 28
Phase III pioglitazone combination [13] Japan [NCT01225081]	Randomised, double-blind, placebo-controlled, parallel group + open-label uncontrolled[a]	Period 1: Ipragliflozin 50 mg QD or placebo with pioglitazone Period 2: Ipragliflozin 50 mg[b] QD with pioglitazone	24 + 28

Table 1 continued

Study descriptionStudy location[ClinicalTrials.gov identifier]	Design	Dosing regimen	Duration (weeks)
Phase III sulfonylurea combination [12] Japan [NCT01242215]	Randomised, double-blind, placebo-controlled, parallel group + open-label uncontrolled[a]	Period 1: Ipragliflozin 50 mg QD or placebo with sulfonylurea Period 2: Ipragliflozin 50 mg[b] QD with sulfonylurea	24 + 28
Phase IV insulin combination [14] Japan [NCT02175784]	Randomised, double-blind, placebo-controlled, parallel group + open-label uncontrolled[a]	Period 1: Ipragliflozin 50 mg QD or placebo with insulin 8–40 units as prescribed Period 2: Ipragliflozin 50 mg[b] QD with insulin 8–40 units as prescribed	16 + 36
Phase III metformin combination [15] Korea, Taiwan [NCT01505426]	Randomised, double-blind, placebo-controlled, parallel group	Ipragliflozin 50 mg QD or placebo with metformin ≥1500 mg QD as prescribed (or ≥ 1000 mg owing to safety concerns)	24
Phase III metformin and sitagliptin combination [16] Korea [NCT02452632]	Randomised, double-blind, placebo-controlled, parallel group	Ipragliflozin 50 mg QD with metformin ≥ 1500 mg QD and sitagliptin 100 mg QD	24
Phase III metformin combination [7] Russia [NCT02794792]	Randomised, double-blind, placebo-controlled, parallel group[a]	Ipragliflozin 50 mg[c] QD or placebo with metformin ≥ 1500 mg QD as prescribed	12 + 12

Table 1 continued

Study description Study location [ClinicalTrials.gov identifier]	Design	Dosing regimen	Duration (weeks)
Phase III long term in patients with renal impairment [8] Japan [NCT01316094]	Randomised, double-blind, placebo-controlled, parallel group + open-label uncontrolled[a]	Period 1: Ipragliflozin 50 mg QD or placebo Period 2: Ipragliflozin 50 mg[b] QD	24 + 28

QD once daily, *BID*, twice daily
[a] Only data from the double-blind period included
[b] Ipragliflozin dose could increase to 100 mg at the beginning of treatment period 2
[c] Ipragliflozin dose could increase to 100 mg

comparative pooled analysis only included data up to 24 weeks. While ipragliflozin is approved at 50 mg and 100 mg doses, only data for patients who received 50 mg were included. Also, some phase II studies used doses that were not taken forward into clinical practice; these studies were excluded as they were not clinically relevant and might have distorted the results.

Treatment Regimens

Ipragliflozin was administered as monotherapy in three studies [5, 6, 9], in combination with metformin in four studies [7, 10, 11, 15], as triple therapy with metformin and dipeptidyl peptidase 4 (DPP4) inhibitors in one study [16], and in combination with pioglitazone [13], sulfonylurea [12] and insulin [14] in one study each (Table 1). In a further study of patients with renal impairment, ipragliflozin was added to existing therapy, which may have consisted of diet and exercise alone, or in combination with an α-glucosidase inhibitor, sulfonylurea or pioglitazone [8].

Ethics

This article is based on analysis of data from previously conducted studies. All procedures followed in the original studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. An independent ethics committee or institutional review board approved the clinical protocol at each participating centre. All participants provided written informed consent prior to inclusion.

Outcomes

TEAEs were analysed for the pooled safety analysis set, consisting of all patients who took at least one dose of ipragliflozin. TEAEs were defined as adverse events (AEs) that occurred after the initiation of study medication. The

definition of TEAEs applied in each individual study was used for the analysis. TEAEs were summarised as follows: overall incidence of TEAEs, number of TEAEs, incidence of drug-related TEAEs, TEAEs leading to permanent discontinuation, serious AEs (SAEs) and TEAEs occurring in at least 2% of the pooled population. A drug-related TEAE was defined as any TEAE with at least a possible relationship to the study treatment as assessed by the investigator, or with missing assessment of the causal relationship.

TEAEs were coded according to preferred terms in the Medical Dictionary for Regulatory Activities [MedDRA] version 19.1 and events recorded in studies using earlier versions of MedDRA were recoded. TEAEs were categorised by the investigators as mild, moderate or severe. Safety outcomes of special interest (hypoglycaemia, renal disorder, volume depletion, UTI, genital infection, pollakiuria or polyuria, CV events, fracture, malignant tumour, skin and subcutaneous tissue disorders) were identified using data captured in the case report form and a list of MedDRA search terms to programmatically identify AEs of interest (see Supplementary Table S1). A medical doctor reviewed all TEAEs, without any treatment information, and judged the relationship to AEs of special interest.

Descriptive subgroup analyses were performed for TEAEs according to ipragliflozin use alone or in combination with other glucose-lowering drug regimens, including metformin, pioglitazone, α-glucosidase inhibitor, sulfonylurea, DPP4 inhibitor, insulin, insulin and DPP4 inhibitor, and metformin and DPP4 inhibitor.

Abnormal laboratory findings (e.g. laboratory parameters, vital signs, electrocardiograms, physical findings) meeting the following criteria were considered AEs: causes clinical signs or symptoms; requires aggressive treatment; requires interruption or discontinuation of the study drug; and physical or laboratory findings considered by the investigator as clinically significant. The levels of ketone bodies were also assessed on the basis of laboratory results.

Statistical Analysis

Descriptive statistics were used to describe safety parameters. All patients who received at least one dose of study treatment were included in the analyses. The analyses were post hoc and no statistical hypothesis testing was performed. All data analyses were performed using SAS Version 9.3.

RESULTS

Patient Demographics

A total of 1209 ipragliflozin (50 mg)-treated patients and 796 placebo-treated patients were included in the pooled analysis. Baseline demographics and clinical characteristics were similar between the two treatment groups (Table 2). The majority of patients were male (59.4%), had a mean age of around 58 years, were overweight (mean body mass index 27.2 kg/m^2) and had a mean duration of T2DM of approximately 8 years.

Summary of Adverse Events

The incidence of TEAEs (Table 3) was similar in patients treated with ipragliflozin (63.8%) and placebo (59.3%). Most TEAEs with ipragliflozin were mild in severity (89.0%), and the incidence of SAEs was very low and similar for ipragliflozin (2.5%) and placebo (3.3%). No SAE occurred in more than two patients. The incidence of TEAEs leading to permanent discontinuation was lower for ipragliflozin (3.6%) than placebo (6.5%). Of the TEAEs that occurred at an incidence of at least 2% (Table 4), the incidence of constipation, pollakiuria and thirst were 2–3.6-fold higher in the ipragliflozin group compared with placebo.

The overall TEAE incidences in patients treated with other doses of ipragliflozin in the pooled comparative trials are shown in Supplementary Table S2. There were no notable differences in the incidence of TEAEs, SAEs or TEAEs leading to permanent discontinuation

Table 2 Patient baseline characteristics of patients treated with ipragliflozin 50 mg or placebo (pooled comparative studies)

Patient characteristics	Ipragliflozin 50 mg (*N* = 1209)	Placebo (*N* = 796)
Sex, *n* (%)		
Female	475 (39.3)	339 (42.6)
Male	734 (60.7)	457 (57.4)
Race, *n* (%)		
White	209 (17.3)	151 (19.0)
Black	9 (0.7)	11 (1.4)
Asian	979 (81.0)	618 (77.6)
Other	12 (1.0)	16 (2.0)
Age (years)	58.1 (10.3)	57.4 (9.9)
Height (cm)	163.9 (9.2)	163.4 (8.9)
Weight (kg)	73.4 (16.1)	72.9 (15.4)
BMI (kg/m^2)	27.2 (4.8)	27.2 (4.8)
BMI, *n* (%)		
< 25 kg/m^2	456 (37.7)	300 (37.7)
≥ 25 kg/m^2	753 (62.3)	496 (62.3)
Disease duration (months)[a]	102.5 (81.9)	97.5 (79.1)
HbA_{1c} (%)[b]	8.19 (0.81)	8.14 (0.82)
eGFR ($mL/min/1.73\ m^2$)[b]	88.8 (29.2)	93.5 (35.6)
eGFR, *n* (%)[b]		
> 90 $mL/min/1.73\ m^2$	483 (40.0)	360 (45.2)
$\geq 60 - < 90$ $mL/min/1.73\ m^2$	627 (51.9)	383 (48.1)
$\geq 30 - < 60$ $mL/min/1.73\ m^2$	96 (8.0)	53 (6.7)
< 30 $mL/min/1.73\ m^2$	1 (0.1)	0 (0)

Data are mean (SD), unless otherwise indicated, in participants who received at least one dose of study drug
BMI body mass index, *HbA_{1c}* glycated haemoglobin A1c, *eGFR* estimated glomerular filtration rate by Modification of Diet in Renal Disease (MDRD) equation
[a] Ipragliflozin, $n = 1201$; placebo, $n = 790$
[b] Ipragliflozin, $n = 1207$; placebo, $n = 796$

Table 3 Overview of adverse events in the pooled ipragliflozin comparative studies

	Ipragliflozin 50 mg (*N* = 1209) ***n*** **(%)**	**Placebo (*N* = 796)** ***n*** **(%)**
TEAE	771 (63.8)	472 (59.3)
Drug-related TEAE	299 (24.7)	135 (17.0)
SAE	30 (2.5)	26 (3.3)
Drug-related SAE	5 (0.4)	6 (0.8)
TEAE leading to discontinuation	44 (3.6)	52 (6.5)
Drug-related TEAE leading to discontinuation	26 (2.2)	14 (1.8)
TEAE severity[a]		
Mild	686 (56.7)	397 (49.9)
Moderate	79 (6.5)	65 (8.2)
Severe	6 (0.5)	10 (1.3)

SAE serious adverse event, *TEAE* treatment-emergent adverse event
[a] Patient counted once under maximum severity

Table 4 Summary of treatment-emergent adverse events that occurred with ipragliflozin treatment at a frequency of at least 2% (by MedDRA preferred term) in the pooled ipragliflozin comparative studies (excluding hypoglycaemia[a])

Adverse event characteristics	**Ipragliflozin 50 mg (*N* = 1209)** ***n*** **(%)**	**Placebo (*N* = 796)** ***n*** **(%)**
Nasopharyngitis	199 (16.5)	117 (14.7)
Pollakiuria	65 (5.4)	12 (1.5)
Constipation	37 (3.1)	12 (1.5)
Thirst	31 (2.6)	6 (0.8)

Participants treated with at least one dose of study drug
MedDRA Medical Dictionary for Regulatory Activities
[a] Hypoglycaemia events are excluded from this summary owing to the effects of other glucose-lowering medications

compared with placebo or with ascending ipragliflozin doses.

Adverse Events of Special Interest

TEAEs related to pollakiuria, volume depletion, genital infection, and skin and subcutaneous tissue disorders were more frequent with ipragliflozin than with placebo (Table 5; see Supplementary Table S1 for AE definition criteria).

Stratification by glucose-lowering medication showed that hypoglycaemia was only increased when ipragliflozin was combined with insulin, owing to the hypoglycaemic effects of insulin (see "Hypoglycaemia-Related Events"), and therefore hypoglycaemia was not considered as a TEAE with increased incidence upon ipragliflozin treatment.

Events consistent with genital infection were experienced by 29 (2.4%) patients in the ipragliflozin group and 5 (0.6%) patients in the placebo group; vulvovaginal candidiasis and genital pruritus were the most commonly reported in the ipragliflozin group (see Supplementary Table S3). Pollakiuria/polyuria-related events occurred in 6.0% of ipragliflozin-treated

Table 5 Incidence of treatment-emergent adverse events of special interest for ipragliflozin (50 mg) in the pooled comparative studies

N (%)	TEAE	Drug-related TEAE	TEAE leading to discontinuation	Drug-related TEAE leading to discontinuation	TEAE severity[a]		
					Mild	Moderate	Severe
Urinary tract infection							
Ipragliflozin	37 (3.1)	27 (2.2)	3 (0.2)	3 (0.2)	4 (0.3)	33 (2.7)	0
Placebo	27 (3.4)	15 (1.9)	0	0	24 (3.0)	3 (0.4)	0
Genital infection							
Ipragliflozin	29 (2.4)	22 (1.8)	1 (0.1)	1 (0.1)	24 (2.0)	4 (0.3)	1 (0.1)
Placebo	5 (0.6)	3 (0.4)	1 (0.1)	1 (0.1)	5 (0.6)	0	0
Pollakiuria or polyuria							
Ipragliflozin	72 (6.0)	65 (5.4)	1 (0.1)	1 (0.1)	70 (5.8)	2 (0.2)	0
Placebo	16 (2.0)	12 (1.5)	0	0	16 (2.0)	0	0
Volume depletion							
Ipragliflozin	59 (4.9)	36 (3.0)	2 (0.2)	2 (0.2)	57 (4.7)	2 (0.2)	0
Placebo	14 (1.8)	5 (0.6)	1 (0.1)	0	12 (1.5)	2 (0.3)	0
Cardiovascular events							
Ipragliflozin	1 (0.1)	0	1 (0.1)	0	0	1 (0.1)	0
Placebo	4 (0.5)	3 (0.4)	3 (0.4)	3 (0.4)	1 (0.1)	0	3 (0.4)
Fracture							
Ipragliflozin	7 (0.6)	0	1 (0.1)	0	4 (0.3)	2 (0.2)	1 (0.1)
Placebo	5 (0.6)	0	0	0	2 (0.3)	3 (0.4)	0
Renal disorder							
Ipragliflozin	11 (0.9)	3 (0.2)	1 (0.1)	0	9 (0.7)	1 (0.1)	1 (0.1)
Placebo	13 (1.6)	5 (0.6)	1 (0.1)	0	13 (1.6)	0	0
Malignant tumours							
Ipragliflozin	3 (0.2)	0	2 (0.2)	0	2 (0.2)	1 (0.1)	0
Placebo	3 (0.4)	1 (0.1)	2 (0.3)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Skin and subcutaneous tissue disorders							
Ipragliflozin	93 (7.7)	31 (2.6)	12 (1.0)	11 (0.9)	85 (7.0)	6 (0.5)	2 (0.2)
Placebo	35 (4.4)	7 (0.9)	1 (0.1)	0	33 (4.1)	2 (0.3)	0

For definitions for adverse events of special interest, see Supplementary Table S1

TEAE treatment-emergent adverse event

[a] Patient counted once under maximum severity

Table 6 Change from baseline in urine ketone levels in the pooled comparative ipragliflozin studies

Time point	Ipragliflozin 50 mg (N = 1209)		Placebo (N = 796)	
	1+ *n* (%)[a]	3+ *n* (%)[b]	1+ *n* (%)[a]	3+ *n* (%)[b]
Baseline	22/1206 (1.8)	4/1206 (0.3)	15/795 (1.9)	1/795 (0.1)
Week 2	72/945 (7.6)	2/945 (0.2)	11/600 (1.8)	0
Week 12	61/1140 (5.4)	7/1140 (0.6)	12/702 (1.7)	0
End of treatment period	58/1202 (4.8)	6/1202 (0.5)	9/792 (1.1)	0

[a] Number of patients with 1+ or higher (2+, 3+ or 4+)/number of patients with available laboratory values at each time point (%)

[b] Number of patients with 3+ or 4+/number of patients with available laboratory values at each time point (%)

Table 7 Incidence of treatment-emergent adverse events related to hypoglycaemia in the pooled comparative ipragliflozin (50 mg) studies stratified by combination with insulin

	No combination		Insulin combinations		Non-insulin combinations		Overall	
	Ipragliflozin 50 mg	Placebo	Ipragliflozin 50 mg	Placebo	Ipragliflozin 50 mg	Placebo	Ipragliflozin 50 mg	Placebo
Hypoglycaemia, *n*/*N* (%)	3/237 (1.3)	2/215 (0.9)	52/175 (29.7)	13/87 (14.9)	21/797 (2.6)	10/494 (2.0)	76/1209 (6.3)	25/796 (3.1)

patients compared with 2.0% of patients in the placebo group (Table 5). Events related to skin and subcutaneous tissue disorders occurred in 7.7% of ipragliflozin-treated patients compared with 4.4% of patients in the placebo group, and were mostly mild in severity (Table 5).

There was a similar incidence of TEAEs related to urinary tract infection in the ipragliflozin and placebo groups (3.1% and 3.4%, respectively, Table 5). The incidence of TEAEs related to CV events was low and similar between the two groups (Table 5; hazard ratio vs placebo 0.28, 95% confidence interval [CI] 0.05–1.57). Four events occurred in the placebo group (acute myocardial infarction, cerebral infarction, thalamic infarction and left ventricular failure) and one event in the group treated with ipragliflozin 50 mg (cerebral infarction).

The proportion of patients who had urine ketone body levels of at least 1+ or 3+ at the end of the treatment period was greater in the ipragliflozin group (4.8% and 0.5%, respectively) than in the placebo group (1.1% and 0%, respectively; Table 6). However, the number of subjects with 3+ ketone levels was small and no TEAE related to ketoacidosis occurred.

Hypoglycaemia-Related Events

Overall, hypoglycaemia-related AEs were more frequent with ipragliflozin than with placebo (6.3% vs 3.1%, respectively; Table 7), but this increase was dependent on background insulin use. The incidence of hypoglycaemia events was similar between ipragliflozin and placebo when they were not combined with any other glucose-lowering drugs (1.3% vs 0.9%, respectively; Table 7). There was a higher incidence of hypoglycaemia compared with placebo when ipragliflozin was combined with insulin (32.4% vs 23.3%, respectively; Supplementary Table S4) or any combination which included insulin (29.7% vs 14.9%, respectively) compared with non-insulin combinations (2.6% vs 2.0%, respectively; Table 7). Overall, hypoglycaemia-related AEs were mild in severity and no drug-related hypoglycaemia-related events led to discontinuation.

DISCUSSION

This pooled analysis confirmed that ipragliflozin is well tolerated in patients with T2DM, with a safety profile consistent with that observed previously for the SGLT2 inhibitor drug class. The incidence of TEAEs, SAEs and TEAEs leading to discontinuation was comparable between the placebo and ipragliflozin treatment groups, and no new safety signals were identified. TEAEs related to pollakiuria, volume depletion, genital infection and skin and subcutaneous tissue disorders were more common after ipragliflozin treatment compared with placebo, while there were similar rates of UTI, CV events, hypoglycaemia renal disorder, fracture and malignant tumours. TEAEs were generally mild in severity and were managed within standard clinical practice.

For patients treated with ipragliflozin monotherapy, there were no drug-related hypoglycaemia events. The low risk for hypoglycaemia is a well-established advantage of the SGLT2 inhibitor drug class, and is consistent with the results of previous pooled and meta-analyses [33, 47–50]. The hypoglycaemia observed with combination therapy is also consistent with a recent pooled analysis of canagliflozin trials, where hypoglycaemia was reported for 6.9% patients receiving canagliflozin monotherapy (100 mg) and 44.4% of patients receiving additional glucose-lowering drugs associated with hypoglycaemia (i.e. insulin, sulfonylurea, glinide) [50]. While a background of sulfonylurea use has been shown previously to increase the risk of hypoglycaemia [47, 48], this was not evident in our subgroup analysis, with very low overall rates of hypoglycaemia with added ipragliflozin (3/218, 1.4%) and placebo (1/96, 1.0%) in patients on sulfonylureas (Supplementary Table S4). Rather, hypoglycaemia in our analysis was almost entirely dependent on background insulin use; rates of drug-related hypoglycaemic events with insulin and non-insulin combinations were 29.1% and 1.0% respectively, suggesting that relative overdose of insulin when combined with ipragliflozin was the cause of hypoglycaemia.

The lack of excess UTI and increased incidence of genital infections with ipragliflozin vs placebo are consistent with results from a meta-analysis of 77 randomised controlled trials of SGLT2 inhibitors which showed no significant risk in UTIs vs control (2526/29,086 vs 1278/14,940; risk ratio [RR] 1.05, 95% CI 0.98–1.12), but an increased risk of genital infections (1521/24,017 vs 216/12,552; RR 3.30, 95% CI 2.74–3.99) [51]. A recent safety announcement issued by the US Food and Drug Administration (FDA) warned that cases of Fournier's gangrene, a rare but serious genital infection, have also been reported with SGLT2 inhibitors [38]. In our analysis, no case of Fournier's gangrene was reported, and TEAEs related to genital infection were generally mild and rarely led to treatment discontinuation.

The number of patients with increased urine ketone body levels (3+) was small and no cases of ketoacidosis were reported. Post-marketing surveillance data for ipragliflozin also suggest a low risk for ketoacidosis, with just one case of diabetic ketoacidosis (0.01%) reported after 24 months, in a large sample of patients in Japan [45]. Although the incidence of ketoacidosis in randomised controlled trials of other SGLT2 inhibitors is also very low [48–50], there is an increased risk compared with placebo (2.2 times greater risk in a recent meta-analysis of CV outcome trials [27]). As a result, drug regulatory agencies have issued warnings about the risk of ketoacidosis with SGLT2 inhibitor use and have provided recommendations to minimise the risk [52, 53].

Osmotic diuresis caused by SGLT2 inhibition may potentially lead to volume depletion in susceptible patients [54]. Indeed, the incidence of volume depletion in our analysis was higher for ipragliflozin compared with placebo (4.9% vs 1.8%). However, these events are mild and have been suggested to reduce over time in a previous study [50]. In a pooled analysis of canagliflozin studies, the majority of volume depletion-related AEs occurred in the first 3 months and then decreased over the course of the next 2 years [50]. In our analysis, the incidence of TEAEs related to renal disorder was similar for ipragliflozin (0.9%) and placebo (1.6%), and the only renal disorder-related TEAE

observed in the ipragliflozin group that was not observed the placebo group was decreased glomerular filtration rate (GFR; $n = 3$, 0.2%: Supplementary Table S3). This is consistent with a recent systematic review of SGLT2 clinical trials and regulatory reports that reported a lack of renal safety signal and emphasised that early volume-related reductions in GFR do not cause significant further reduction in renal function [33]. Furthermore, the CREDENCE trial has demonstrated renal protection with canagliflozin in patients with T2DM and chronic kidney disease, over a median follow-up of 2.62 years, despite early reductions in estimated GFR [25]. Evaluation of long-term renal function is limited in the present analysis by the 24-week timeframe.

While ipragliflozin has been reported to improve many cardiometabolic risk factors in patients with T2DM [22], investigation of any cardioprotective effects will require long-term intervention and follow-up. In the EMPA-REG OUTCOME trial [23], the composite endpoint of death from CV causes, non-fatal myocardial infarction and non-fatal stroke decreased by 14% ($P = 0.04$) in patients treated with empagliflozin after a median follow-up of 3.1 years. CV benefits have also been reported in long-term outcome studies for canagliflozin [24] and dapagliflozin [26] and in a large, global, real-world study of SGLT2 inhibitors, including ipragliflozin, vs other glucose-lowering drugs [55]. Compared with the patients with established CV diseases in previous outcomes trials, the patient population in our pooled analysis had a relatively low CV risk. While ipragliflozin was associated with fewer CV-related TEAEs than placebo, overall rates were low (one event in ipragliflozin group vs four events in the placebo group). Thus, the low CV risk and the short timeframe limit any meaningful interpretation of data regarding cardioprotective effects of ipragliflozin in the present analysis.

An FDA Advisory Committee have already raised concerns regarding a potential dapagliflozin-associated risk of bladder and breast cancer [36]. However, meta-analyses of the current evidence from clinical studies of SGLT2 inhibitors [33, 35, 56] have not identified an overall increased cancer risk, and a recent large-scale dapagliflozin study ($n = 17,160$) has shown statistically lower rates of bladder cancer compared with placebo [26]. Consistent with this, our pooled analysis showed no marked increase in the incidence of any type of cancer. However, given the relatively short-term nature of the studies, further monitoring of the long-term effects of ipragliflozin may be required to continue.

Fracture and lower limb amputation was included as an outcome based on findings from the canagliflozin clinical trials, CANVAS study and CANVAS-R study, which have reported increased incidence of fracture and an approximate two-fold increase in lower limb amputation [24]. However, consistent with the pooled safety findings for empagliflozin and dapagliflozin [48, 49] and results of a more recent clinical outcomes study for canagliflozin (CREDENCE study [25]), no increase in fracture was identified with ipragliflozin and no case of lower limb amputation occurred.

Skin and subcutaneous tissue disorders were increased with ipragliflozin treatment in the present study (7.7% in ipragliflozin treatment group vs 4.4% in placebo group), with an incidence approximately 3.3% higher than placebo. Hypersensitivity AEs with SGLT2 inhibitors have been reported previously in some patients, including a recent report of dermatological AEs in Japan [39]. In a recent pooled analysis of hypersensitivity-related skin AEs for dapagliflozin, the most common skin events were rash (1.1% with dapagliflozin vs 1.1% with active or placebo comparator), eczema (0.6% vs 0.8%), dermatitis (0.5% vs 0.4%) and urticaria (0.5% vs 0.2%), with few patients discontinuing as a result of hypersensitivity AEs ($\leq$ 0.2%) [42]. Consistent with these findings, eczema and skin rash were the most common events reported with ipragliflozin in the present study (Supplementary Table S5). Interim results of an ipragliflozin post-marketing surveillance study in Japan (STELLA-LONG TERM), which included a safety analysis set comprising 11,051 patients, reported 147 cases (1.3%) of skin and subcutaneous tissue disorders after 1 year of follow-up [46]. Skin lesions are reported to be well controlled after stopping ipragliflozin and administration of appropriate anti-inflammatory

drugs. Furthermore, a sub-analysis in the present study revealed that Asian patients with diabetes in both the ipragliflozin and placebo groups had a higher incidence of skin disorder events than non-Asian patients with diabetes (Supplementary Table S5). This differs from the dapagliflozin data, which shows no difference in the incidence of serious hypersensitivity reaction between Asian and non-Asian patients [42]. There have been few studies investigating the potential mechanisms for SGLT2 inhibitor-related skin lesions and the exact mechanisms remain unknown. One study has reported that ipragliflozin is retained in the skin of rats at a relatively higher concentration compared with other SGLT2 inhibitors [41]. Furthermore, cluster analysis of an in silico 3-D docking simulation indicated a stable ipragliflozin–melanin complex, suggesting a possible role for melanin in ipragliflozin-specific skin and subcutaneous tissue disorders [41]. In any case, accumulation of further clinical case studies will be important for the elucidation of the exact mechanisms.

A major limitation of our pooled safety analysis was the limited patient numbers and short-term duration of the trials, all of which lasted for a maximum of 24 weeks for the placebo comparison. Although the incidence of AEs is often higher at the start of a trial, and would not be affected by the short duration of the trials, some outcomes of special interest, such as CV events and cancer, will require longer-term follow-up data to determine any meaningful results. It should be noted that all trials included patients with T2DM only and findings may not apply to T1DM, for which ipragliflozin is also indicated. Also, while ipragliflozin is approved at 50 mg and 100 mg doses, only data for patients who received 50 mg were included in the pooled analysis, owing to the relatively small patient numbers for the 100 mg dose in comparative studies ($n = 72$ for 100 mg vs $n = 1209$ for the 50 mg dose). The summary AE data per dose (Supplementary Table S2) suggest similar incidences between the 50 mg and 100 mg doses for TEAEs (63.8% and 56.9%, respectively), drug-related TEAEs (24.7% vs 25.0%) and TEAEs leading to discontinuation (3.6% vs 4.2%).

Limitations of the pooled methodology include the post hoc nature of the present analyses and outcome definitions that might not be identical across all the studies. Furthermore, the findings from highly selected patient populations in clinical studies do not always reflect real-world outcomes, thus limiting the generalisability of the findings. However, it is noteworthy that the latest findings from ongoing post-marketing surveillance programmes for ipragliflozin support the pooled clinical trial data reported here [44–46].

CONCLUSION

This pooled analysis of randomised, placebo-controlled trials has confirmed that ipragliflozin is well tolerated in patients with T2DM, with a safety profile consistent with that observed previously for the SGLT2 inhibitor drug class and post-marketing surveillance data. No new safety concerns were identified, confirming that ipragliflozin is well tolerated when used alone or in combination with other glucose-lowering agents.

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Compliance with Ethics Guidelines. This article is based on analysis of data from previously conducted studies. All procedures followed in the original studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. An independent ethics committee or institutional review board approved the clinical protocol at each participating centre. All participants provided written informed consent prior to inclusion.

Data Availability. For studies NCT00621868 and NCT01505426, access to anonymized individual participant level data will not be provided as it meets one or more of the exceptions described on http://www.clinicalstudydatarequest.com under "Sponsor Specific Details for Astellas." For all other studies, access to anonymized individual participant level data collected during the study, in addition to supporting clinical documentation, is planned for studies conducted with approved product indications and formulations, as well as compounds terminated during development. Studies conducted with product indications or formulations that remain active in development are assessed after study completion to determine if Individual Participant Data can be shared. Conditions and exceptions are described under the Sponsor Specific Details for Astellas on http://www.clinicalstudydatarequest.com. Study-related supporting documentation is redacted and provided if available, such as the protocol and amendments, statistical analysis plan and clinical study report. Access to participant level data is offered to researchers after publication of the primary manuscript (if applicable) and is available as long as Astellas has legal authority to provide the data. Researchers must submit a proposal to conduct a scientifically relevant analysis of the study data. The research proposal is reviewed by an Independent Research Panel. If the proposal is approved, access to the study data is provided in a secure data sharing environment after receipt of a signed Data Sharing Agreement.

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