ORIGINAL ARTICLE

Safety and tolerability of empagliflozin in East Asian patients with type 2 diabetes: Pooled analysis of phase I–III clinical trials

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ABSTRACT

Aims/Introduction: We investigated the safety and tolerability of empagliflozin (EMPA) in East Asian patients with type 2 diabetes.

Materials and Methods: Data were pooled from participants with type 2 diabetes evenly randomized to a placebo, EMPA 10 mg or EMPA 25 mg in 15 phase I–III trials. Adverse events (AEs) were analyzed in the subgroup of trial participants from East Asian countries/regions.

Results: In total, 709, 724 and 708 East Asian trial participants with type 2 diabetes received a placebo, EMPA 10 mg and EMPA 25 mg, respectively; total exposure was 953, 1,072, and 1,033 patient-years in these groups, respectively. The EMPA and placebo groups had similar incidences of severe AEs, serious AEs and AEs leading to discontinuation. Incidences of hypoglycemia differed according to anti-diabetes medication used at baseline. Higher rates of events consistent with genital infection were observed with EMPA (EMPA 1.5–1.7/100, placebo 0.2/100 patient-years). Rates of AEs consistent with volume depletion were comparable among treatment groups (0.8–1.4/100 patient-years), but in trial participants aged ≥65 years, the rate was greater with EMPA 25 mg (EMPA 25 mg 3.5/100, placebo 2.0/100 patient-years). Incidences of events consistent with urinary tract infection, thromboembolic events, renal events, hepatic AEs, diabetic ketoacidosis, fractures and lower limb amputation were similar between EMPA and the placebo.

Conclusions: In the present pooled analysis, EMPA was well tolerated in East Asian type 2 diabetes patients based on >2,100 patient-years' exposure, consistent with results from the overall analysis population.

INTRODUCTION

The burden of diabetes in Asia is increasing rapidly. Between 2017 and 2045, the number of people living with diabetes is projected to increase from 159 to 183 million in the Western Pacific region, with a significant proportion from East Asia[1]. Compared with Caucasians, East Asians develop type 2 diabetes at a younger age, with more visceral adiposity at any given body mass index and have more significant pancreatic β-cell dysfunction[2–5].

Empagliflozin (EMPA) is a selective sodium–glucose cotransporter 2 inhibitor (SGLT2i) used in type 2 diabetes management. In a pooled data analysis of four phase III trials, 24-week EMPA monotherapy or add-on therapy ameliorated glycemic control, reduced body weight and blood pressure, and was well tolerated in trial participants with type 2 diabetes from Asian countries[6]. In the EMPA-REG OUTCOME® trial, EMPA in addition to standard care reduced the risks of cardiovascular death, all-cause mortality, hospitalization for heart failure and the incidence or worsening of nephropathy, and led to significant reductions in the urinary albumin-to-creatinine ratio in type 2 diabetes trial participants with established cardiovascular

disease[7–9]. Reductions in the risk of cardiovascular outcomes, all-cause mortality and the incidence or worsening of nephropathy with EMPA in Asian trial participants were consistent with those of the overall population[8,10]. Reductions in cardiovascular outcomes and all-cause mortality risks were consistent between East Asian and the overall population[10].

Empagliflozin was well tolerated when data were pooled and assessed from type 2 diabetes studies, including trial participants that were evenly randomized to EMPA 10 mg, EMPA 25 mg, or a placebo in 15 phase I–III clinical trials[11]. Trial participants from the Asian region comprised approximately one-quarter of trial participants in that analysis[11]. As the pathophysiology of diabetes and comorbidities may differ in East Asian trial participants compared with other ethnic groups, a comprehensive evaluation of the safety of EMPA in East Asian trial participants is desirable to better inform clinical practice in this population[4,12]. We report here on the safety and tolerability of EMPA in the subgroup of East Asian trial participants with type 2 diabetes from the large pool of data from placebo-controlled clinical trials.

METHODS

Patients
Data were pooled from 15 phase I–III clinical trials plus four extension trials[7,13–30], of which 10 trials included trial participants of Asian race from five East Asian countries/regions (i.e., China, Hong Kong, Taiwan, Korea and Japan; Table S1)[7,13–15,19,23,25,27,28,30].

Statistical analysis
The safety and tolerability of EMPA in the subgroup of Asian trial participants from five East Asian countries/regions (i.e., China, Hong Kong, Taiwan, Korea and Japan) were analyzed. Adverse events (AEs) reported by investigators and coded using preferred terms in the Medical Dictionary for Regulatory Activities version 18.0 were assessed. A severe AE was defined as an AE judged by the investigator to be incapacitating or causing inability to work or to carry out usual activities. A serious AE (SAE) was defined as an AE that resulted in death, was immediately life-threatening, resulted in persistent or marked disability/incapacity, required or prolonged patient hospitalization, was a congenital anomaly/birth defect, or was deemed serious for any other reason. Safety topics of special interest included: confirmed hypoglycemic AEs (plasma glucose ≤3.9 mmol/L and/or requiring assistance); events consistent with urinary tract infection (UTI); events consistent with genital infection; events consistent with volume depletion (VD); events consistent with diabetic ketoacidosis; decreased renal function; hepatic AEs; fractures; and lower limb amputations. We manually reviewed the pooled data and AE narratives to assess lower limb amputation, which is not typically included in AE reports. We also assessed laboratory parameters including hematocrit, hemoglobin, urine ketone levels (dipstick test, based on worst recorded value on treatment), renal and hepatic parameters, electrolytes, bone markers (alkaline phosphatase, 25-hydroxy vitamin D, urinary N-telopeptide/creatinine ratio, parathyroid hormone) and lipids.

Adverse events in trial participants receiving ≥1 dose of the study drug were analyzed using descriptive statistics. Exposure-adjusted incidence rates were calculated per 100 patient-years as $100 \times n/T$, where n was the number of trial participants with the event, and T was the total patient-years at risk of the event. Patient-years at risk were defined as the time from the first dose to the onset of the first event for trial participants with an event or to the last dose +7 days for those without an event. Incidence rate ratios and 95% confidence intervals (CI) were analyzed using a Cochran–Mantel–Haenszel test.

RESULTS

Patient disposition, exposure and baseline characteristics
A total of 709, 724 and 708 trial participants from East Asian countries/regions received placebo, EMPA 10 mg or EMPA 25 mg, respectively. Total exposure was 953 patient-years in the placebo group, 1,072 patient-years in the EMPA 10 mg group, and 1,033 patient-years in the EMPA 25 mg group. Baseline demographics and clinical characteristics of East Asian trial participants were similar among the three groups (Table 1). Mean (SD) age was 58.0 (10.2) years, mean (SD) BMI was 25.7 (3.5) kg/m^2, and time after type 2 diabetes diagnosis was >5 years in 59.5% of East Asian trial participants.

Summary of adverse events
In East Asian trial participants with type 2 diabetes, the placebo group had similar incidences of severe AEs, SAEs, and AEs leading to discontinuation compared with the EMPA groups (Table 2; Figure 1). Compared to the EMPA groups, the incidence rates of common AEs were comparable in the placebo group, except for hypoglycemia (Table 2).

Hypoglycemia
The incidence of confirmed hypoglycemic AEs was comparable between EMPA and placebo in the overall East Asian analysis population (Figure 1; Table 3), but was different according to the anti-diabetes drugs used at baseline. The incidence of confirmed hypoglycemic AEs was low in all treatment groups when given as monotherapy (Table 3). The incidence of confirmed hypoglycemic AEs was higher in the two EMPA groups compared to placebo in trial participants taking insulin at baseline. In trial participants taking sulfonylurea (SU) or metformin at baseline, the incidence of confirmed hypoglycemic AEs was higher in the EMPA 10 mg than placebo, while it was comparable between EMPA 25 mg and placebo (Table 3).

UTI
Compared with the placebo, the EMPA groups had a similar incidence of events consistent with UTI in East Asian trial participants (Table 4; Figure 1). In all groups, females had a higher incidence than males, but the incidence was comparable between EMPA and the placebo regardless of sex (Table 4). Events

Table 1 | Demographics and baseline characteristics of East Asian trial participants

	Placebo (*n* = 709)	EMPA 10 mg (*n* = 724)	EMPA 25 mg (*n* = 708)
Male	450 (63.5)	498 (68.8)	485 (68.5)
Age (years)	58.3 ± 10.1	58.0 ± 9.9	57.7 ± 10.6
<50	141 (19.9)	155 (21.4)	156 (22.0)
50 to <65	374 (52.8)	372 (51.4)	362 (51.1)
≥65	194 (27.4)	197 (27.2)	190 (26.8)
Country			
Japan	213 (30.0)	223 (30.8)	223 (31.5)
China	196 (27.6)	194 (26.8)	190 (26.8)
Korea	185 (26.1)	195 (26.9)	185 (26.1)
Taiwan	89 (12.6)	88 (12.2)	91 (12.9)
Hong Kong	26 (3.7)	24 (3.3)	19 (2.7)
Time since diagnosis (years)			
≤1	63 (8.9)	73 (10.1)	80 (11.3)
>1 to 5	192 (27.1)	191 (26.4)	177 (25.0)
>5 to 10	190 (26.8)	159 (22.0)	169 (23.9)
>10	187 (26.4)	221 (30.5)	211 (29.8)
Missing	77 (10.9)	80 (11.0)	71 (10.0)
Number of background glucose-lowering medications			
0	292 (41.2)	297 (41.0)	289 (40.8)
1	113 (15.9)	118 (16.3)	125 (17.7)
2	221 (31.2)	226 (31.2)	217 (30.6)
3	66 (9.3)	74 (10.2)	64 (9.0)
4	16 (2.3)	7 (1.0)	10 (1.4)
5	1 (0.1)	2 (0.3)	3 (0.4)
BMI (kg/m^2)[†]	25.8 ± 3.5	25.6 ± 3.5	25.7 ± 3.6
HbA1c (%)	7.99 ± 0.78	7.94 ± 0.77	7.94 ± 0.79
FPG (mmol/L)[‡]	8.25 ± 1.79	8.20 ± 1.79	8.23 ± 1.83
SBP (mmHg)[§]	130.1 ± 15.4	129.9 ± 15.6	129.1 ± 15.5
DBP (mmHg)[§]	77.9 ± 9.6	77.9 ± 9.6	77.8 ± 9.5
eGFR (mL/min/1.73 m²)	85.9 ± 19.9	87.8 ± 20.3	87.4 ± 19.4
≥90	275 (38.8)	312 (43.1)	299 (42.2)
60 to <90	377 (53.2)	364 (50.3)	368 (52.0)
30 to <60	57 (8.0)	48 (6.6)	41 (5.8)
<30	0	0	0

Data are *n* (%) or mean ± standard deviation in trial participants who received at least one dose of the study drug. [†]Placebo *n* = 688; empagliflozin (EMPA) 10 mg *n* = 704; EMPA 25 mg *n* = 689. [‡]Placebo *n* = 706; EMPA 10 mg *n* = 722; EMPA 25 mg *n* = 705. [§]Placebo *n* = 667; EMPA 10 mg *n* = 684; EMPA 25 mg *n* = 670. BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate by Modification of Diet in Renal Disease equation; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; SBP, systolic blood pressure; T2DM, type 2 diabetes.

consistent with UTI were mild or moderate, except for two severe UTIs in the placebo group. Events consistent with UTI led to treatment discontinuation in 0.3, 0.1 and 0% of trial participants in the placebo, EMPA 10 mg and EMPA 25 mg groups, respectively. The proportion of trial participants with UTIs reported as SAEs was low (placebo 0.4%, EMPA 10 mg 0% and EMPA 25 mg 0%). No complicated UTIs (urosepsis, pyelonephritis or SAEs consistent with UTI) were reported in the EMPA groups, whereas 0.4% had these events in the placebo group. There were no pyelonephritis cases in all three groups.

Genital infection

The EMPA groups had a higher incidence of events consistent with genital infection in East Asian trial participants (Table 4; Figure 1). This was consistent in male and female trial participants, although females had higher incidence than males in all three groups (Table 4). The genital infection events were mild or moderate in severity, and only 0.1% of participants in the EMPA 10 mg group discontinued the treatment due to a genital infection. There were no genital infections reported as SAEs in the three groups.

VD

The EMPA and placebo groups had a similar incidence of events consistent with VD in East Asian trial participants (Table 4; Figure 1). This pattern was observed across age subgroups, apart from a higher incidence with EMPA 25 mg (3.5/100 patient-years) than the placebo (2.0/100 patient-years) in

Table 2 | Summary of adverse events in East Asian trial participants

	Placebo (*n* = 709)		EMPA 10 mg (*n* = 724)		EMPA 25 mg (*n* = 708)	
	n (%)	Rate/100 patient-years	*n* (%)	Rate/100 patient-years	*n* (%)	Rate/100 patient-years
≥1 AE	507 (71.5)	183.6	510 (70.4)	150.3	491 (69.4)	135.0
≥1 drug-related AE†	125 (17.6)	15.0	175 (24.2)	20.3	145 (20.5)	16.4
≥1 AE leading to discontinuation	51 (7.2)	5.4	41 (5.7)	3.8	47 (6.6)	4.6
≥1 severe AE‡	61 (8.6)	6.8	44 (6.1)	4.2	48 (6.8)	4.8
≥1 serious AE§	114 (16.1)	13.8	105 (14.5)	10.8	107 (15.1)	11.7
Fatal AE	5 (0.7)	0.5	3 (0.4)	0.3	6 (0.8)	0.6
AEs with frequency of ≥5% in any group (by MedDRA preferred term)						
Hypoglycemia	67 (9.4)	7.7	97 (13.4)	10.4	76 (10.7)	8.2
Hyperglycemia	94 (13.3)	10.9	28 (3.9)	2.7	27 (3.8)	2.6
Nasopharyngitis	86 (12.1)	9.9	85 (11.7)	8.6	83 (11.7)	8.8
Upper respiratory tract infection	65 (9.2)	7.3	54 (7.5)	5.4	74 (10.5)	7.8
Urinary tract infection	58 (8.2)	6.5	50 (6.9)	4.9	44 (6.2)	4.5
Dizziness	51 (7.2)	5.7	44 (6.1)	4.3	47 (6.6)	4.8

Data from trial participants treated with at least one dose of study drug. †In opinion of investigator. ‡Adverse event (AE) that is incapacitating or causing inability to work or to carry out usual activities. §AE that results in death, is immediately life-threatening, results in persistent or significant disability/incapacity, requires or prolongs patient hospitalization, is a congenital anomaly/birth defect, or is deemed serious for any other reason. AE, adverse event; EMPA, empagliflozin; MedDRA, Medical Dictionary for Regulatory Activities.
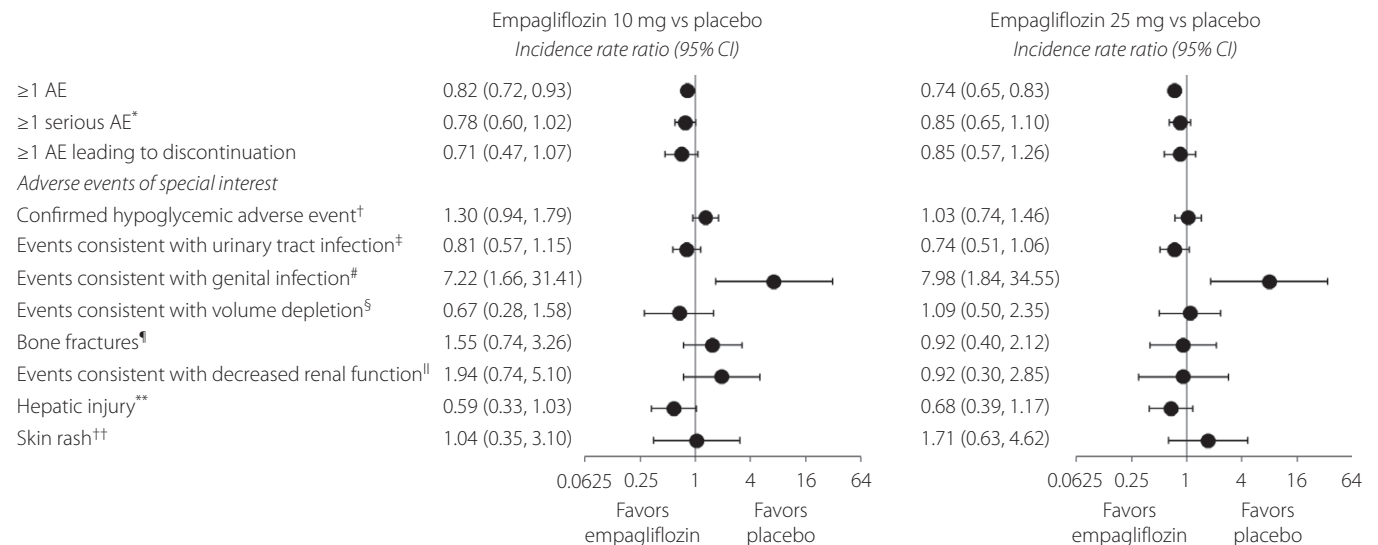

Figure 1 | Adverse events (AEs) in East Asian trial participants. *AE that results in death, is immediately life-threatening, results in persistent or significant disability/incapacity, requires or prolongs patient hospitalization, is a congenital anomaly/birth defect, or is deemed serious for any other reason. †Plasma glucose 3.9 mmol/L and/or requiring assistance. ‡Based on 79 MedDRA preferred terms; 10 were reported, of which urinary tract infection, cystitis, bacteriuria and asymptomatic bacteriuria were the most frequent. #Based on 88 MedDRA preferred terms; 15 were reported, of which vaginal infection, balanoposthitis, genital infection and vulvovaginal candidiasis were the most frequent. §Based on eight MedDRA preferred terms; five were reported, of which hypotension, syncope, orthostatic hypotension and dehydration were the most frequent. ¶Based on 62 MedDRA preferred terms; 23 were reported, of which rib fracture, ankle fracture, facial bones fracture, femoral neck fracture, hand fracture and tibia fracture were the most frequent. ‖Based on the narrow standardized MedDRA query (SMQ; 'acute renal failure' for decreased renal function). **Based on four narrow sub-SMQs. ††Based on 18 MedDRA preferred terms; three were reported, of which rash was the most frequent. CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities.

trial participants aged ≥65 years (Table 4). In trial participants using diuretics at baseline, the incidence of events consistent with VD was comparable between the placebo and EMPA

25 mg, but lower with EMPA 10 mg. In the subgroup of trial participants who were using loop diuretics at baseline, events consistent with VD were reported in two trial participants in

Table 3 | Confirmed hypoglycemic adverse events[†] in East Asian trial participants

	Placebo (n = 709)			EMPA 10 mg (n = 724)			EMPA 25 mg (n = 708)		
	n or n/N	%	Rate/100 patient-years	n or n/N	%	Rate/100 patient-years	n or n/N	%	Rate/100 patient-years
Confirmed hypoglycemia[†]	63	8.9	7.1	88	12.2	9.2	69	9.7	7.3
Background glucose-lowering medication use									
No	0/292	0	0	1/297	0.3	0.4	4/289	1.4	2.0
Yes	63/417	15.1	8.8	87/427	20.4	12.0	65/419	15.5	8.8
Insulin use[‡]									
No	46/645	7.1	5.8	56/650	8.6	6.5	46/642	7.2	5.5
Yes	17/64	26.6	17.9	32/74	43.2	32.1	23/66	34.8	22.6
Sulfonylurea use[‡]									
No	12/436	2.8	3.0	27/464	5.8	5.4	25/447	5.6	5.4
Yes	51/273	18.7	10.4	61/260	23.5	13.5	44/261	16.9	9.3
Metformin use[‡]									
No	10/339	2.9	3.9	16/341	4.7	5.4	19/351	5.4	6.0
Yes	53/370	14.3	8.4	72/383	18.8	10.9	50/357	14.0	8.1

Data from trial participants who received at least one dose of study drug. [†]Plasma glucose ≤3.9 mmol/L and/or requiring assistance. [‡]With or without other glucose-lowering medication. EMPA, empagliflozin.

the EMPA 25 mg group and none in the placebo or EMPA 10 mg groups. The proportion of trial participants with VD reported as a SAE was low (placebo 0.1%, EMPA 10 mg 0%, EMPA 25 mg 0.1%). The incidence of dehydration (MedDRA preferred term) was low and comparable in the three groups (Table 4).

Hematocrit and venous thromboembolic events
Hemoglobin and hematocrit were increased in the EMPA groups, but not in the placebo group (Table 5). The three groups showed similarly low incidence of venous thromboembolic events (0.2/100 patient-years; Table 4).

Diabetic ketoacidosis
Compared with the placebo group, greater proportions of trial participants in the EMPA groups showed at least 1+ urinary ketones (Table 6). However, the proportion of diabetic ketoacidosis was low in the three groups (placebo, n = 2 [0.3%]; EMPA 10 mg, n = 1 [0.1%]; EMPA 25 mg, n = 0 [0%]; Table 4). There were no reports of treatment discontinuation due to diabetic ketoacidosis or diabetic ketoacidosis related to study drug as judged by investigators, and all trial participants recovered. There were small changes in bicarbonate levels in each group, which were not deemed to be clinically meaningful (Table 5).

Renal function and laboratory parameters
Estimated glomerular filtration rate (eGFR), according to the Modification of Diet in Renal Disease equation, was decreased in the placebo group, whereas it was increased in the EMPA 25 mg group and was not changed in the EMPA 10 mg group (Table 5). The incidence of events consistent with decreased renal function was similar in the three groups

(Table 4; Figure 1). Acute kidney injury (MedDRA preferred term) was observed in the placebo and EMPA 10 mg groups (placebo, n = 1; and EMPA 10 mg, n = 1), but not in the EMPA 25 mg group (Table 4). The EMPA groups had greater decreases in serum uric acid than the placebo groups (Table 5). The three groups had similar incidence of nephrolithiasis (Placebo, 0.7; EMPA 10 mg, 0.3; and EMPA 25 mg 0.4 per 100 patient-years), renal colic (placebo 0, EMPA 10 mg 0.1 and EMPA 25 mg 0 per 100 patient-years) or gout (placebo 0.6, EMPA 10 mg 0.4 and EMPA 25 mg 0.4 per 100 patient-years).

Hepatic function and laboratory parameters
The EMPA groups had a similar incidence of events consistent with hepatic injury compared with the placebo in East Asian trial participants (Table 4; Figure 1). Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase or bilirubin did not show any clinically relevant changes in any group (Table 5). Clinically relevant elevation in ALT and/or AST was rare in the three groups (Table 7). Only one trial participant in the EMPA 25 mg group had ALT and AST at least threefold the upper limit of normal and bilirubin at least twofold the upper limit of normal (Table 6); this case did not meet Hy's Law criteria.

Electrolytes, parathyroid hormone and bone fractures
No clinically meaningful changes were observed in serum electrolytes or bone markers, such as alkaline phosphatase, 25-hydroxy vitamin D, urinary N-telopeptide/creatinine ratio and parathyroid hormone in the three groups (Table 5). There was a similar incidence of bone fractures in all groups (placebo 1.2, EMPA 10 mg 1.8 and EMPA 25 mg 1.1 per 100 patient-years; Table 4; Figure 1).

Table 4 | Adverse events of special interest

	Placebo (n = 709)			EMPA 10 mg (n = 724)			EMPA 25 mg (n = 708)		
	n or n/N	%	Rate/100 patient-years	n or n/N	%	Rate/100 patient-years	n or n/N	%	Rate/100 patient-years
Events consistent with urinary tract infection[†]	64	9.0	7.2	59	8.1	5.8	52	7.3	5.3
Sex									
Male	15/450	3.3	2.4	22/498	4.4	2.9	8/485	1.6	1.1
Female	49/259	18.9	18.0	37/226	16.4	14.5	44/223	19.7	17.7
Events consistent with genital infection[‡]	2	0.3	0.2	16	2.2	1.5	17	2.4	1.7
Sex									
Male	1/450	0.2	0.2	8/498	1.6	1.0	2/485	0.4	0.3
Female	1/259	0.4	0.3	8/226	3.5	2.8	15/223	6.7	5.2
Events consistent with volume depletion[§]	12	1.7	1.3	9	1.2	0.8	14	2.0	1.4
Age									
<50 years	1/141	0.7	0.7	2/155	1.3	1.0	0/156	0	0
50 to <65 years	5/374	1.3	1.0	1/372	0.3	0.2	4/362	1.1	0.8
≥65 years	6/194	3.1	2.0	6/197	3.0	1.8	10/190	5.3	3.5
Diuretic use at baseline									
Yes	4/76	5.3	2.7	1/92	1.1	0.5	6/91	6.6	3.3
No	8/633	1.3	1.0	8/632	1.3	0.9	8/617	1.3	1.0
Loop diuretic use at baseline									
Yes	0/16	0	0	0/22	0	0	2/21	9.5	4.0
No	12/693	1.7	1.3	9/702	1.3	0.9	12/687	1.7	1.2
Dehydration	2	0.3	0.2	2	0.3	0.2	2	0.3	0.2
Bone fractures[¶]	11	1.6	1.2	19	2.6	1.8	11	1.6	1.1
Events consistent with decreased renal function[††]	6	0.8	0.6	13	1.8	1.2	6	0.8	0.6
Acute kidney injury[‡‡]	1	0.1	0.1	1	0.1	0.1	0	0	0
Hepatic injury[§§]	30	4.2	3.2	20	2.8	1.9	22	3.1	2.2
Diabetic ketoacidosis[¶¶]	2	0.3	0.2	1	0.1	0.1	0	0	0
Venous thromboembolic events[†††]	2	0.3	0.2	2	0.3	0.2	2	0.3	0.2
Skin rash[‡‡‡]	6	0.8	0.6	7	1.0	0.7	11	1.6	1.1
Lower limb amputations[§§§]	0	0	0	1	0.1	0.1	0	0	0
Events potentially related to lower limb amputations									
Peripheral artery obstructive disease events	7	1.0	0.7	6	0.8	0.6	3	0.4	0.3
Diabetic foot-related events	1	0.1	0.1	0	0	0	0	0	0
Relevant infection events	4	0.6	0.4	5	0.7	0.5	4	0.6	0.4
Wound events	2	0.3	0.2	2	0.3	0.2	3	0.4	0.3

Data from trial participants who received at least one dose of study drug. [†]Based on 79 MedDRA preferred terms, 10 were reported, of which urinary tract infection, cystitis, bacteriuria and asymptomatic bacteriuria were the most frequent. [‡]Based on 88 MedDRA preferred terms, 15 were reported, of which vaginal infection, balanoposthitis, genital infection and vulvovaginal candidiasis were the most frequent. [§]Based on eight MedDRA preferred terms (blood pressure decreased, blood pressure ambulatory decreased, blood pressure systolic decreased, dehydration, hypotension, orthostatic hypotension, hypovolemia, syncope), five were reported, of which hypotension, syncope, orthostatic hypotension and dehydration were the most frequent. [¶]Based on 62 MedDRA preferred terms, 23 were reported, of which rib fracture, ankle fracture, facial bones fracture, femoral neck fracture, hand fracture and tibia fracture were the most frequent. [††]Based on the narrow standardized MedDRA query (SMQ; "acute renal failure" for decreased renal function). [‡‡]MedDRA preferred term. [§§]Based on four narrow sub-SMQs. [¶¶]Based on two MedDRA preferred terms. [†††]Based on 1 narrow SMQ. [‡‡‡]Based on 18 MedDRA preferred terms, three were reported, of which rash was the most frequent. [§§§]Those reported as an adverse event, those reported as a "medical procedure" in electronic clinical report forms or in investigator comments describing adverse events, or those identified from a systematic search of serious adverse event narratives. The definitions are identical with other Boehringer Ingelheim studies including overall analysis[11]. AE, adverse event; eGFR, estimated glomerular filtration rate by Modification of Diet in Renal Disease equation; EMPA, empagliflozin; MedDRA, Medical Dictionary for Regulatory Activities.

Serum lipids

Serum levels of total, high-density lipoprotein cholesterol (HDL-cholesterol) and low-density lipoprotein cholesterol (LDL-cholesterol), as well as LDL-cholesterol/HDL- cholesterol ratio and triglyceride levels did not show any relevant changes in the three groups in East Asian trial participants (Table 5). Similarly, no relevant changes in apolipoproteins A-I and B were observed (Table 5).

Table 5 | Laboratory results

	Placebo			EMPA 10 mg			EMPA 25 mg		
	n	Baseline	Change from baseline[†]	*n*	Baseline	Change from baseline[†]	*n*	Baseline	Change from baseline[†]
Hematocrit (%)	682	42.6 ± 4.9	−0.0 ± 3.7	704	42.6 ± 4.9	3.4 ± 4.1	681	43.0 ± 5.0	3.1 ± 4.2
Hemoglobin (g/L)	682	139 ± 14	−1 ± 9	705	139 ± 14	8 ± 10	682	140 ± 14	7 ± 11
Uric acid (μmol/L)	680	298 ± 122	−7 ± 85	706	289 ± 120	−33 ± 83	681	292 ± 114	−38 ± 86
Serum creatinine (μmol/L)	685	79 ± 17	1 ± 12	709	78 ± 15	1 ± 11	687	78 ± 16	0 ± 10
eGFR (mL/min/1.73 m^2)	684	85.8 ± 19.9	−0.5 ± 11.8	709	87.7 ± 20.2	−0.0 ± 11.7	687	87.5 ± 19.3	0.5 ± 12.6
Aspartate aminotransferase (U/L)	685	17 ± 14	−2 ± 13	709	15 ± 11	−2 ± 10	687	16 ± 12	−1 ± 16
Alanine aminotransferase (U/L)	685	22 ± 19	−3 ± 16	709	20 ± 16	−4 ± 13	687	20 ± 15	−3 ± 21
Alkaline phosphatase (U/L)	685	64 ± 28	1 ± 21	709	63 ± 26	−1 ± 14	687	64 ± 27	−2 ± 15
Total bilirubin (μmol/L)	682	10.5 ± 3.8	−0.1 ± 3.2	706	10.6 ± 3.6	−0.2 ± 2.8	682	10.8 ± 3.5	−0.3 ± 3.3
25-hydroxy vitamin D (nmol/L)[‡]	199	75.9 ± 30.5	−1.1 ± 31.7	213	79.2 ± 31.0	−0.0 ± 29.4	205	77.6 ± 31.3	5.1 ± 32.4
Urinary N-telopeptide/creatinine ratio (nmol/L : mmol/L Cre)[‡]	193	45 ± 24	−2 ± 16	206	42 ± 20	3 ± 16	195	44 ± 20	8 ± 29
Parathyroid hormone (pmol/L)[‡]	198	4.1 ± 1.5	−0.1 ± 1.2	213	4.2 ± 1.5	0.1 ± 1.2	205	4.6 ± 6.1	−0.3 ± 5.4
Electrolytes									
Sodium (mmol/L)	680	141 ± 2	−0 ± 2	706	141 ± 2	0 ± 2	681	141 ± 2	0 ± 2
Potassium (mmol/L)	679	4.1 ± 0.3	0.0 ± 0.3	706	4.1 ± 0.3	−0.0 ± 0.3	680	4.1 ± 0.3	−0.0 ± 0.3
Calcium (mmol/L)	680	2.4 ± 0.1	−0.0 ± 0.1	706	2.4 ± 0.1	−0.0 ± 0.1	681	2.4 ± 0.1	−0.0 ± 0.1
Magnesium (mmol/L)	680	1.0 ± 0.1	−0.0 ± 0.1	706	1.0 ± 0.1	0.0 ± 0.1	681	1.0 ± 0.1	0.0 ± 0.1
Phosphate (mmol/L)	680	1.2 ± 0.1	0.0 ± 0.1	706	1.2 ± 0.1	0.0 ± 0.1	681	1.2 ± 0.1	0.0 ± 0.1
Bicarbonate (mmol/L)	679	24.4 ± 2.6	0.0 ± 2.9	705	24.5 ± 2.6	−0.4 ± 2.9	681	24.5 ± 2.6	−0.7 ± 3.0
Total cholesterol (mmol/L)	643	4.6 ± 1.1	0.1 ± 0.8	667	4.6 ± 1.1	0.2 ± 0.8	649	4.7 ± 1.2	0.2 ± 0.8
HDL cholesterol (mmol/L)	643	1.3 ± 0.4	0.0 ± 0.2	667	1.3 ± 0.3	0.1 ± 0.2	649	1.3 ± 0.4	0.1 ± 0.2
LDL cholesterol (mmol/L)	638	2.6 ± 0.9	0.0 ± 0.7	656	2.5 ± 0.9	0.1 ± 0.7	643	2.6 ± 1.0	0.1 ± 0.7
LDL/HDL cholesterol ratio	638	2.1 ± 0.9	−0.0 ± 0.6	656	2.0 ± 0.8	−0.1 ± 0.6	643	2.1 ± 0.9	−0.1 ± 0.6
Triglycerides (mmol/L)	643	1.7 ± 1.2	0.0 ± 1.2	667	1.8 ± 1.5	−0.1 ± 1.4	649	1.8 ± 1.8	−0.1 ± 1.4
Apolipoprotein A-I (g/L)	580	1.3 ± 0.1	0.0 ± 0.1	601	1.3 ± 0.1	0.0 ± 0.1	594	1.3 ± 0.1	0.0 ± 0.1
Apolipoprotein B (g/L)	580	1.1 ± 0.6	0.0 ± 0.4	601	1.1 ± 0.6	0.0 ± 0.4	594	1.1 ± 0.6	0.1 ± 0.4

Data are mean ± standard deviation in trial participants who received at least one dose of the study drug and had laboratory values available at baseline and on treatment. Data are normalized to a standard reference range, except for estimated glomerular filtration (eGFR) and lipids. [†]Change from baseline at last value on treatment. [‡]Urinary N-telopeptide/creatinine ratio, 25-hydroxy vitamin D and parathyroid hormone levels were only recorded in two monotherapy trials[19,27]. EMPA, empagliflozin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 6 | Dipstick urine ketone levels: worst recorded measurement on treatment

	Placebo (*n* = 633)	EMPA 10 mg (*n* = 658)	EMPA 25 mg (*n* = 636)
Negative	531 (83.9)	467 (71.0)	419 (65.9)
Trace	69 (10.9)	98 (14.9)	95 (14.9)
1+	27 (4.3)	65 (9.9)	89 (14.0)
2+	4 (0.6)	23 (3.5)	28 (4.4)
3+	2 (0.3)	5 (0.8)	5 (0.8)

Data are *n* (%) in trial participants who received at least one dose of study drug and had ketone values available at baseline and on treatment. EMPA, empagliflozin.

Lower limb amputations

There was one case of lower limb amputation among East Asian trial participants in the EMPA 10 mg group (Table 4).

In all three groups, there was a similar incidence of events that could potentially be related to amputations (Table 4).

Skin rash

The incidence of skin rash in East Asian participants was low and generally comparable between EMPA 10 mg and the placebo (Figure 1; Table 4). Although incidence rate ratio included 1.0, a numerical increase was observed with EMPA 25 mg. No severe and serious skin rash was reported in all groups.

DISCUSSION

The current analysis of pooled safety data based on >2,100 patient-years' exposure to EMPA was carried out to evaluate the safety and tolerability of EMPA in East Asian trial participants. Our analyses show that EMPA is well tolerated in East Asian trial participants. The AE profile in East Asian trial participants receiving EMPA generally agreed

Table 7 | Elevations in liver enzymes and bilirubin

	Placebo (n = 709)	EMPA 10 mg (n = 724)	EMPA 25 mg (n = 708)
ALT and/or AST ≥3 × ULN	15 (2.1)	3 (0.4)	7 (1.0)
ALT and/or AST ≥5 × ULN	2 (0.3)	1 (0.1)	3 (0.4)
ALT and/or AST ≥3 × ULN with bilirubin ≥2 × ULN	0	0	1 (0.1)

Data are n (%) in trial participants who received at least one dose of the study drug. ALT, alanine aminotransferase; AST, aspartate aminotransferase; EMPA, empagliflozin; ULN, upper limit of normal.

with the profile reported in the overall pooled analysis population[11].

In the overall population, the hypoglycemia risk was not increased with EMPA, except in trial participants on background SU[11]. SUs are associated with an increased hypoglycemia risk, as they stimulate insulin secretion[31]. In analyses of other SGLT2 inhibitors given in combination with a SU, an increased risk of hypoglycemia has been reported[32,33]. In East Asian trial participants, the incidence of confirmed hypoglycemic AEs was higher with EMPA 10 and 25 mg when compared with the placebo in trial participants taking insulin at baseline, and was generally comparable with EMPA and the placebo in trial participants taking SU or metformin at baseline. Considering its insulin-independent mechanism of action, an increased hypoglycemia risk would not be expected with EMPA[34], but when EMPA is co-administered with a SU or insulin, a lower dose of the SU or insulin should be considered to reduce hypoglycemia risk[35–38].

The incidence of UTIs was lower in both male and female East Asian trial participants compared with the overall analysis population. Consistent with the overall analysis population[11] and EMPA-REG OUTCOME® trial[7,10], the incidence of UTIs was similar between EMPA and the placebo.

The overall rate of genital infections was lower in East Asian trial participants compared with the overall analysis population irrespective of sex. The possible explanation for this finding remains unknown. Consistent with the overall population, the incidence of these events in East Asian trial participants was higher with EMPA; however, these events were mostly mild or moderate and were rarely the cause for the discontinuation of treatment.

EMPA causes transient natriuresis and increases urine volume[39,40], which might increase the VD risk, especially in the elderly or those taking diuretics. In the present analysis, the incidence of events consistent with VD was similar between EMPA and the placebo in East Asian trial participants, including participants taking diuretics. The incidence of these events was greater in elderly trial participants in all treatment groups compared with younger trial participants and, consistent with the overall population[11], the incidence was also greater with EMPA than the placebo. A similar trend has been observed in studies with other SGLT2i drugs. The post-marketing studies of the SGLT2is, ipragliflozin and tofogliflozin, in elderly Japanese type 2 diabetes patients, showed that age ≥75 years was associated with a higher risk of VD compared with an age of <75 years[41,42]. The potential for VD in patients receiving EMPA, particularly in elderly patients, is acknowledged in the prescribing information[35–38]. Although hematocrit was increased in East Asian trial participants treated with EMPA, there was no increase in venous thromboembolic events.

The incidence of ketonuria was slightly higher in East Asian trial participants treated with EMPA, as would be expected in trial participants with induced glucosuria, and lower glucose and insulin levels. However, the incidence of diabetic ketoacidosis in this pool of East Asian trial participants was low and not increased with EMPA compared with the placebo; these results are consistent with the overall population. The incidence of events consistent with hepatic injury was not increased with EMPA in East Asian trial participants. This is particularly important given the high prevalence of non-alcoholic fatty liver disease (NAFLD), chronic viral hepatitis B and hepatitis C in East Asia[43–45]. Strong associations between NAFLD and diabetes have been reported in East Asia[43]. Recently, it was shown that hepatic fat measured by magnetic resonance imagine-derived proton density fat fraction and serum ALT level was significantly reduced with EMPA in Indian patients with NAFLD[46]. Some studies suggest that SGLT2is ameliorate fatty liver in Japanese patients with type 2 diabetes[47,48]. Hepatitis B infection in the Asian population results in chronic low-grade inflammation, which increases the risk of β-cell dysfunction, chronic kidney disease and cancer, whereas hepatitis C is frequently associated with diabetes[5,49,50].

A small decrease in eGFR was observed in East Asian trial participants in the placebo group, whereas a small increase was observed in the EMPA 25 mg group, and no changes were observed in the EMPA 10 mg group. In the EMPA-REG OUTCOME® trial, eGFR initially decreased, but then remained stable in the EMPA groups; whereas eGFR declined steadily in the placebo group[8,10]. At the post-treatment follow-up visit, eGFR increased in the EMPA groups, such that eGFR was significantly higher with EMPA than the placebo[8]. These observations suggest that the initial decreases in eGFR are due to hemodynamic effects of EMPA, and EMPA may slow the decline in renal function in type 2 diabetes trial participants[8]. The incidence of events consistent with decreased renal function was not increased with EMPA in the present analysis of East Asian trial participants; these results are consistent with both EMPA-REG OUTCOME®[7] and the overall pooled analysis population[11].

There had been hypotheses that SGLT2is might increase bone fracture risks due to modulation of renal calcium and phosphate reabsorption[51,52]. Consistent with the overall population, the incidence of bone fractures was not increased in East Asian trial participants receiving EMPA. In the EMPA groups, there were no clinically relevant changes in levels of calcium, those of phosphate or other bone markers. In 4-year data from a small substudy of the head-to-head study of EMPA versus glimepiride as an add-on to metformin (EMPA-REG H2H-SU trial), the mean femoral neck and lumbar spine T-scores remained in the normal range in the EMPA 25 mg group at weeks 52, 104, 156 or 208[53]. Also, there were no significant differences between EMPA 25 mg and glimepiride groups in changes from baseline in femoral neck or lumbar spine T-scores, or in bone mineral content at the same time-points.

One patient receiving EMPA had a lower limb amputation in this pooled analysis of East Asian trial participants with type 2 diabetes. An increased risk of lower limb amputation with the SGLT2i, canagliflozin, was observed in the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program in trial participants with type 2 diabetes and high cardiovascular risk[54]. No such increase was observed in the EMPA-REG OUTCOME trial of EMPA in type 2 diabetes trial participants with established cardiovascular disease[55].

Previously, it was reported that the incidence of skin disorders was higher with some SGLT2is than DPP4 inhibitors in Japan[12]. In this analysis, the incidence of skin rash was generally comparable between the placebo and EMPA 10 mg, whereas a numerical imbalance was seen with EMPA 25 mg compared with the placebo in East Asian trial participants. The vast majority of skin reactions were mild, but not severe or serious. In addition, serious skin disorders defined from 77 skin-related AEs were not associated with EMPA in the Japanese Adverse Drug Event Report database provided by the Pharmaceuticals and Medical Devices Agency (PMDA)[56]. However, allergic skin reactions; that is, skin rash, are considered a side-effect for EMPA, as per prescribing information[35].

The strengths of the analysis include the large cohort of trial participants from East Asia and the length of exposure. Limitations of this analysis are that the duration of the studies was variable and that, although this was a large cohort, the numbers of trial participants in some subgroup analyses were small, and the results of those analyses should be interpreted with caution. The analysis of lower limb amputations should be interpreted with caution, as such cases were retrieved and validated manually. Bone fragility might develop over a longer period than the treatment periods of the trials used in the present analysis. We did not assess bone mineral density in the trials.

In conclusion, in the current analysis of pooled safety data from placebo-controlled trials, EMPA was well tolerated in East Asian type 2 diabetes patients based on >2,100 patient-years' exposure, consistent with results from the overall pooled analysis population.

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SUPPORTING INFORMATION

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

Table S1 | Numbers of East Asian trial participants with type 2 diabetes from placebo-controlled trials included in the pooled analysis.