Original Research

Safety and Tolerability of Empagliflozin in Patients with Type 2 Diabetes

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ABSTRACT

Purpose: The aim of this analysis was to establish the safety profile and tolerability of empagliflozin in patients with type 2 diabetes mellitus (T2DM) according to pooled data from several clinical trials.

Methods: Pooled data were analyzed from patients with T2DM treated with placebo (n = 3695), empagliflozin 10 mg (n = 3806), or empagliflozin 25 mg (n = 4782) in 17 randomized, Phase I, II, and III clinical trials plus 6 extension studies. Adverse events (AEs) were assessed descriptively in patients who took ≥1 dose of the study drug. AE incidence rates per 100 patient-years were calculated to adjust for differences in drug exposure across trials.

Findings: Total exposure was 3254, 3840, and 5649 patient-years in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively. The incidence of any AEs, AEs leading to treatment discontinuation, severe AEs, and serious AEs was no higher in patients treated with empagliflozin than with placebo. Empagliflozin was not associated with an increased risk of hypoglycemia versus placebo, except in patients on background sulfonylurea and/or insulin. The incidence of events consistent with urinary tract infection was similar across treatment groups (9.4–11.3/100 patient-years); 0.4%, 0.2%, and 0.3% of patients in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively, had urinary tract infections that required or prolonged hospitalization. The incidence of events consistent with genital infection was higher in patients treated with empagliflozin (4.7 and 5.0/100 patient-years for empagliflozin 10 and 25 mg, respectively) than placebo (1.3/100 patient-years), but only 0.1%, 0.1%, and <0.1% in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively, had genital infections that required or prolonged hospitalization. The incidence of AEs consistent with volume depletion was similar with placebo, empagliflozin 10 mg, and empagliflozin 25 mg (1.6, 1.5, and 1.3/100 patient-years, respectively) and was higher with empagliflozin 25 mg than placebo or empagliflozin 10 mg in patients aged >75 years (4.4 vs 2.3 and 2.5/100 patient-years, respectively). The incidences of bone fractures, malignancies, decreased renal function, hepatic injury, venous thromboembolic events, and diabetic ketoacidosis were low and similar across the treatment groups.

Implications: In this predefined analysis that was based on >9000 patient-years' exposure to empagliflozin, empagliflozin 10 mg, and empagliflozin 25 mg were well tolerated in patients with T2DM. (*Clin Ther.* 2016;38:1299–1313) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: adverse drug event, hypoglycemia, ketoacidosis, safety, SGLT2 inhibitor.

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Accepted for publication March 22, 2016.
http://dx.doi.org/10.1016/j.clinthera.2016.03.031
0149-2918/$ - see front matter

INTRODUCTION

Empagliflozin is a potent and selective sodium glucose cotransporter 2 (SGLT2) inhibitor[1] used in the treatment of type 2 diabetes mellitus (T2DM). By reducing renal glucose reabsorption and so increasing urinary glucose excretion, inhibiting SGLT2 leads to a reduction in hyperglycemia in patients with T2DM.[2] The mechanism of action of SGLT2 inhibitors is independent of β-cell function; therefore, SGLT2 inhibitors are associated with a low risk of hypoglycemia.[2]

In Phase III trials, empagliflozin (10 and 25 mg) used as monotherapy or as add-on to commonly used antidiabetes drug regimens was associated with improvements in glycemic control and reductions in weight and blood pressure versus placebo.[3–8] In these trials, empagliflozin was well tolerated with no increase in confirmed hypoglycemic events compared with placebo, except as add-on to sulfonylurea or fixed-dose insulin.[3–9] Adverse events (AEs) consistent with urinary tract infection (UTI) were reported in similar proportions of patients on empagliflozin and placebo, but AEs consistent with genital infections were reported in greater proportions of patients on empagliflozin than placebo.[3–9] In this study, we present a comprehensive analysis of safety profile data pooled from 17 Phase I to III clinical trials plus 6 extension studies of empagliflozin in patients with T2DM that was undertaken to characterize the safety profile and tolerability of empagliflozin. Analyzing data pooled from several studies improves the precision of incidence estimates of AEs by enlarging the sample size and can identify tolerability signals that may be difficult to detect in smaller studies.[10] AE incidence rates per 100 patient-years were calculated to adjust for differences in drug exposure across trials.

PATIENTS AND METHODS

Patient Population

For this analysis, data were pooled from all randomized controlled, blinded Phase I to III clinical trials of empagliflozin in patients with T2DM. Pooled safety profile data were analyzed from patients with T2DM treated with empagliflozin 10 or 25 mg in 16 randomized, Phase I to III clinical trials of 8 days' to 104 weeks' duration,[3–9,11–19] plus 6 extension studies,[20–25] plus an interim analysis of data from a Phase III cardiovascular outcomes trial.[26] Patients who received active comparators in these studies were not included in the analysis.

Assessments

This pooled analysis of AEs was planned and prespecified before the completion of the studies. Assessment of safety profile and tolerability was based on AEs reported by the investigator (coded according to the Medical Dictionary for Regulatory Activities [MedDRA] version 16.1) and clinical laboratory tests. Predefined AEs of special interest included confirmed hypoglycemic AEs (plasma glucose ≤ 3.9 mmol/L and/or requiring assistance); events consistent with UTI, genital infection, and volume depletion; bone fractures; malignancies; decreased renal function; and hepatic injury. Events consistent with UTI, genital infection, and volume depletion were assessed through a search of 77, 89, and 8 MedDRA preferred terms, respectively. Bone fractures were assessed through a search of 60 MedDRA preferred terms. Malignancies, decreased renal function, and hepatic injury were assessed based on 2, 1, and 4 standardized MedDRA queries, respectively. Diabetic ketoacidosis (DKA) and venous thromboembolic events were assessed based on searches of 3 and 5 MedDRA preferred terms, respectively. AEs classified as severe, serious, or related to the study drug were as reported by the investigator. A severe AE was one judged to be incapacitating or causing inability to work or to perform usual activities. A serious AE was one 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 that was based on appropriate medical judgment.

Data Analysis

Predefined analyses of AEs were conducted using data from patients who received ≥ 1 dose of the study drug, including patients who were re-randomized to receive empagliflozin 10 or 25 mg in an extension study. AEs were analyzed using descriptive statistics. AE frequencies were calculated (n [%]), and exposure-adjusted incidence rates were calculated per 100 patient-years $= 100 \times n/T$, where n was the number of subjects with the specified event and T was the total patient-years. Patient-years were defined as the time from the first dose to the onset of the first event (for patients with an event) or to the last dose (for patients without an event).

The frequency of confirmed hypoglycemic AEs was analyzed by background antidiabetes medication using descriptive statistics. Data were analyzed

from patients randomized to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily for 24 weeks as monotherapy or as add-on to metformin, add-on to metformin plus sulfonylurea, or add-on to pioglitazone with or without metformin, and from patients who received empagliflozin for 78 weeks as add-on to basal insulin or for 52 weeks as add-on to daily multiple doses of insulin (MDIs).[3–7,18]

Laboratory values (except elevations in liver enzymes and bilirubin relative to the upper limit of normal [ULN]) were analyzed in all patients who received ≥1 dose of the study drug, excluding patients who switched to empagliflozin 10 or 25 mg in an extension study. Elevations in liver enzymes and bilirubin relative to ULN were analyzed in patients who received ≥1 dose of the study drug, including patients who switched to empagliflozin 10 or 25 mg in an extension study. Estimated glomerular filtration rate (eGFR; according to the Modification of Diet in Renal Disease equation) over time was analyzed in patients with T2DM and chronic kidney disease (CKD) who completed 52 weeks of treatment with empagliflozin or placebo in a Phase III randomized trial.[15] In that trial, patients with CKD stage 2 (eGFR ≥60 and <90 mL/min/1.73 m^2) were randomized to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo, and patients with CKD stage 3 (eGFR ≥30 to <60 mL/min/1.73 m^2) or CKD stage 4 (eGFR ≥15 to <30 mL/min/1.73 m^2) were randomized to receive empagliflozin 25 mg or placebo.[15] Laboratory data were analyzed using descriptive statistics.

RESULTS

Patient Disposition, Baseline Characteristics, and Exposure

In total, 3695 patients received placebo, 3806 received empagliflozin 10 mg, and 4782 received empagliflozin 25 mg, including patients who were re-randomized to receive empagliflozin 10 or 25 mg in an extension study. Baseline demographic and clinical characteristics were generally balanced between the treatment groups with the exception of the number of background antidiabetes medications (Table I; not including patients who were re-randomized to receive empagliflozin 10 or 25 mg in an extension study). Total exposure was 3254, 3840, and 5649 patient-years in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively.

Summary of Adverse Events

The exposure-adjusted incidence of AEs, AEs considered drug-related by the investigator, and AEs leading to treatment discontinuation are shown in Table II. The incidence of severe AEs, serious AEs, and fatal AEs was higher in the placebo group than in the empagliflozin groups. The most common AEs occurred at similar or higher incidence rates in the placebo group than in the empagliflozin groups, except for pollakiuria (Table II).

Hypoglycemia

The incidence of confirmed hypoglycemic AEs depended on background medication (Table III). When used as monotherapy, add-on to metformin, or add-on to pioglitazone with or without metformin, the percentage of patients with confirmed hypoglycemic AEs was low in all groups (Table III). When empagliflozin was used as add-on to metformin plus sulfonylurea, the incidence of confirmed hypoglycemic AEs was higher with empagliflozin than with placebo (Table III). No confirmed hypoglycemic AEs that required assistance were reported in these studies (Table III).

When empagliflozin was used as add-on to fixed-dose basal insulin, the percentage of patients with confirmed hypoglycemic AEs was higher with empagliflozin 25 mg than with placebo or empagliflozin 10 mg (Table III). Likewise, when empagliflozin was used as add-on to fixed-dose MDI, the percentage of patients with confirmed hypoglycemic AEs was higher with empagliflozin 10 and 25 mg than with placebo. When empagliflozin was added to flexible doses of basal insulin or MDI, the percentage of patients with confirmed hypoglycemic AEs was similar in all treatment groups (Table III).

UTI

The incidence of events consistent with UTI was similar in the placebo and empagliflozin groups (11.3, 10.4, and 9.4/100 patient-years in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively). The incidence of events consistent with UTI was much higher in female than male patients in all treatment groups, but was similar between empagliflozin and placebo in both male and female patients (Table IV). Events consistent with UTI were mild or moderate in 98% of patients who experienced them and led to premature treatment discontinuation in a small proportion of patients (0.2%, 0.4%, and 0.3%

Table I. Demographic and baseline characteristics.

	Placebo (n = 3695)	Empagliflozin 10 mg (n = 3487)	Empagliflozin 25 mg (n = 4465)
Male, n (%)	2301 (62.3)	2208 (63.3)	2793 (62.6)
Age, years	60.3 (9.8)	60.1 (9.7)	59.6 (10.1)
Race, n (%)			
White	2346 (63.5)	2250 (64.5)	2869 (64.3)
Asian	1164 (31.5)	1068 (30.6)	1404 (31.4)
Black/African-American	157 (4.2)	140 (4.0)	163 (3.7)
Other*	26 (0.7)	25 (0.7)	24 (0.5)
Missing	2 (0.1)	4 (0.1)	5 (0.1)
Time since diagnosis of T2DM, years, n (%)			
≤1	211 (5.7)	229 (6.6)	312 (7.0)
>1 to 5	836 (22.6)	762 (21.9)	1115 (25.0)
>5	2627 (71.1)	2472 (70.9)	3012 (67.5)
Missing	21 (0.6)	24 (0.7)	26 (0.6)
Background antidiabetes medications, n (%)			
0	420 (11.4)	404 (11.6)	413 (9.2)
1	1162 (31.4)	1084 (31.1)	1887 (42.3)
2	1578 (42.7)	1487 (42.6)	1600 (35.8)
Other	535 (14.5)	512 (14.7)	565 (12.7)
Weight, kg	85.0 (19.7)	85.0 (20.0)	84.8 (19.8)
BMI, kg/m^2	30.3 (5.5)	30.4 (5.7)	30.3 (5.6)
HbA_{1c}, %	8.06 (0.83)	8.06 (0.84)	8.02 (0.83)
FPG, mmol/L	8.5 (2.3)	8.5 (2.3)	8.5 (2.2)
SBP, mm Hg	134.1 (16.8)	133.5 (16.2)	133.7 (16.4)
DBP, mm Hg	77.8 (9.7)	77.9 (9.6)	78.0 (9.4)
eGFR, mL/min/1.73m^2	77.6 (22.6)	80.1 (21.5)	79.5 (22.3)
eGFR, mL/min/1.73m^2, n (%)			
≥90	1015 (27.5)	1019 (29.2)	1362 (30.5)
60 to <90	1908 (51.6)	1902 (54.5)	2310 (51.7)
30 to <60	718 (19.4)	554 (15.9)	732 (16.4)
<30	52 (1.4)	7 (0.2)	56 (1.3)
Missing	2 (0.1)	5 (0.1)	5 (0.1)

Data are mean (SD), unless otherwise indicated. Data from patients who received ≥1 dose of the study drug, not including patients who switched to empagliflozin 10 mg or 25 mg in an extension study.
BMI = body mass index; eGFR = estimated glomerular filtration rate by Modification of Diet in Renal Disease equation; DBP = diastolic blood pressure; FPG = fasting plasma glucose; Hb_{A1c} = glycosylated hemoglobin; SBP = systolic blood pressure; T2DM = type 2 diabetes mellitus.
*American Indian/Alaska Native/Hawaiian/Pacific Islander.

in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively). The proportion of patients with events consistent with UTI that required or prolonged hospitalization was similar in the placebo and empagliflozin groups (0.4%, 0.2%, and 0.3% in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively). The percentage of patients with events consistent with UTI was similar

Table II. Summary of AEs.

	Placebo (n = 3695)		Empagliflozin 10 mg (n = 3806)		Empagliflozin 25 mg (n = 4782)	
	n (%)	Rate/100 patient-years	n (%)	Rate/100 patient-years	n (%)	Rate/100 patient-years
≥1 AE	2621 (70.9)	215.1	2686 (70.6)	176.3	3499 (73.2)	167.1
≥1 Investigator-reported drug-related AE	636 (17.2)	22.6	845 (22.2)	26.7	1063 (22.2)	22.7
≥1 AE leading to discontinuation	208 (5.6)	6.4	191 (5.0)	5.0	255 (5.3)	4.5
≥1 Severe AE[*]	324 (8.8)	10.4	258 (6.8)	6.9	373 (7.8)	6.8
≥1 Serious AE[†]	494 (13.4)	16.4	393 (10.3)	10.7	573 (12.0)	10.8
Deaths	29 (0.8)	0.9	19 (0.5)	0.5	26 (0.5)	0.5
AEs with frequency of ≥2% in any group (by preferred term)						
Hypoglycemia	602 (16.3)	21.1	597 (15.7)	17.6	677 (14.2)	13.2
Nasopharyngitis	290 (7.8)	9.4	345 (9.1)	9.6	420 (8.8)	7.9
Urinary tract infection	285 (7.7)	9.2	316 (8.3)	8.7	433 (9.1)	8.1
Hyperglycemia	426 (11.5)	14.4	211 (5.5)	5.7	304 (6.4)	5.6
Upper respiratory tract infection	158 (4.3)	5.0	162 (4.3)	4.3	273 (5.7)	5.0
Back pain	135 (3.7)	4.2	136 (3.6)	3.6	221 (4.6)	4.0
Dizziness	112 (3.0)	3.5	141 (3.7)	3.8	196 (4.1)	3.6
Headache	116 (3.1)	3.6	117 (3.1)	3.1	195 (4.1)	3.5
Diarrhea	131 (3.5)	4.1	137 (3.6)	3.6	172 (3.6)	3.1
Influenza	101 (2.7)	3.1	83 (2.2)	2.2	160 (3.3)	2.9
Arthralgia	113 (3.1)	3.5	111 (2.9)	2.9	158 (3.3)	2.9
Hypertension	161 (4.4)	5.1	107 (2.8)	2.8	156 (3.3)	2.8
Bronchitis	109 (2.9)	3.4	102 (2.7)	2.7	124 (2.6)	2.2
Pollakiuria	39 (1.1)	1.2	90 (2.4)	2.4	121 (2.5)	2.2
Dyslipidemia	94 (2.5)	2.9	95 (2.5)	2.5	119 (2.5)	2.1
Cough	116 (3.1)	3.6	82 (2.2)	2.2	117 (2.4)	2.1
Pain in extremity	80 (2.2)	2.5	85 (2.2)	2.2	107 (2.2)	1.9
Edema peripheral	74 (2.0)	2.3	28 (0.7)	0.7	40 (0.8)	0.7

Data are n (%) in patients who received ≥1 dose of the study drug, including patients who switched to empagliflozin 10 mg or 25 mg in an extension study.
AE = adverse event.
[*]AE that is incapacitating or causing inability to work or to perform 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 based on appropriate medical judgment.

between empagliflozin and placebo in patients with or without a history of chronic or recurrent UTI. However, events consistent with UTI were reported by a higher proportion of patients with a history of chronic or recurrent UTI (27.8%, 25.7%, and 29.9% in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively) than in patients without such a history (8.8%, 9.1%, and

Table III. Confirmed hypoglycemic adverse events by study.

	Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
Monotherapy (24 weeks; Roden 2013), n	229	224	223
Confirmed hypoglycemic adverse events*	1 (0.4)	1 (0.4)	1 (0.4)
Requiring assistance	0	0	0
Add-on to metformin (24 weeks; Haering 2014), n	206	217	214
Confirmed hypoglycemic adverse events*	1 (0.5)	4 (1.8)	3 (1.4)
Requiring assistance	0	0	0
Add-on to metformin + sulfonylurea (24 weeks; Haering 2013), n	225	224	217
Confirmed hypoglycemic adverse events*	19 (8.4)	36 (16.1)	25 (11.5)
Requiring assistance	0	0	0
Add-on to pioglitazone ± metformin (24 weeks; Kovacs 2014), n	165	165	168
Confirmed hypoglycemic adverse events*	3 (1.8)	2 (1.2)	4 (2.4)
Requiring assistance	0	0	0
Add-on to basal insulin (18 weeks/78 weeks†; Rosenstock 2015), n	170	169	155
18 weeks			
Confirmed hypoglycemic adverse events*	35 (20.6)	33 (19.5)	44 (28.4)
Requiring assistance	0	0	1 (0.6)
78 weeks			
Confirmed hypoglycemic adverse events*	60 (35.3)	61 (36.1)	56 (36.1)
Requiring assistance	0	0	2 (1.3)
Add-on to MDI ± metformin (18 weeks/52 weeks‡; Rosenstock 2014), n	188	186	189
18 weeks			
Confirmed hypoglycemic adverse events*	70 (37.2)	74 (39.8)	78 (41.3)
Requiring assistance	1 (0.5)	1 (0.5)	1 (0.5)
52 weeks			
Confirmed hypoglycemic adverse events*	109 (58.0)	95 (51.1)	109 (57.7)
Requiring assistance	3 (1.6)	3 (1.6)	1 (0.5)

Data are n (%) in patients who received ≥1 dose of the study drug.
MDI = multiple dose of insulin.
*Plasma glucose ≤3.9 mmol/L and/or requiring assistance.
†The dose of insulin was to remain stable in weeks 1 to 18 then be adjusted during weeks 19 to 78 to meet glucose target.
‡The dose of insulin was to be stable in weeks 1 to 18, adjusted to meet glucose targets in weeks 19 to 40, then stable in weeks 41 to 52.

9.3%, respectively). Acute pyelonephritis was reported in 0.1% of patients on placebo and <0.1% in each empagliflozin group. Urosepsis was reported in 0.1%, 0.1%, and <0.1% of patients in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively. All patients with urosepsis recovered.

Genital Infection

The incidence of events consistent with genital infection was higher in patients treated with empagliflozin than with placebo (1.3, 4.7, and 5.0/100 patient-years in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively). The incidence of events consistent with genital infection

Table IV. AEs of special interest.

AE event	Placebo (N = 3695) n (%) or n/N (%)	Placebo (N = 3695) Rate/100 patient-years	Empagliflozin 10 mg (N = 3806) n (%) or n/N (%)	Empagliflozin 10 mg (N = 3806) Rate/100 patient-years	Empagliflozin 25 mg (N = 4782) n (%) or n/N (%)	Empagliflozin 25 mg (N = 4782) Rate/100 patient-years
AEs consistent with urinary tract infection*	344 (9.3)	11.3	374 (9.8)	10.4	497 (10.4)	9.4
Sex						
Male	75/2301 (3.3)	3.8	93/2417 (3.8)	3.9	137/2987 (4.6)	4.0
Female	269/1394 (19.3)	25.3	281/1389 (20.2)	22.8	360/1795 (20.1)	19.2
AEs consistent with genital infection†	41 (1.1)	1.3	177 (4.7)	4.7	268 (5.6)	5.0
Sex						
Male	18/2301 (0.8)	0.9	83/2417 (3.4)	3.5	112/2987 (3.7)	3.3
Female	23/1394 (1.6)	1.8	94/1389 (6.8)	6.8	156/1795 (8.7)	7.7
AEs consistent with volume depletion‡	51 (1.4)	1.6	57 (1.5)	1.5	74 (1.5)	1.3
Age						
<50 years	4/495 (0.8)	0.9	2/560 (0.4)	0.3	9/769 (1.2)	0.9
50 to <65 years	21/1953 (1.1)	1.2	22/2014 (1.1)	1.1	25/2483 (1.0)	0.8
65 to <75 years	21/1011 (2.1)	2.5	28/1012 (2.8)	2.9	28/1251 (2.2)	2.1
>75 years	5/236 (2.1)	2.3	5/220 (2.3)	2.5	12/279 (4.3)	4.4
Diuretic use at baseline						
Yes	27/1190 (2.3)	2.5	30/1167 (2.6)	2.6	41/1439 (2.8)	2.6
No	24/2505 (1.0)	1.1	27/2639 (1.0)	1.0	33/3343 (1.0)	0.8
Loop diuretic use at baseline						
Yes	10/352 (2.8)	3.2	14/279 (5.0)	5.6	12/376 (3.2)	3.4
No	41/3343 (1.2)	1.4	43/3527 (1.2)	1.2	62/4406 (1.4)	1.2
Bone fractures§	67 (1.8)	2.1	66 (1.7)	1.7	63 (1.3)	1.1
eGFR ≥90 mL/min/1.73m^2	7/1015 (0.7)	0.8	19/1143 (1.7)	1.6	27/1474 (1.8)	1.5
eGFR 60 to <90 mL/min/1.73m^2	36/1908 (1.9)	2.2	31/2094 (1.5)	1.5	23/2500 (0.9)	0.8
eGFR 45 to <60 mL/min/1.73m^2	18/479 (3.8)	4.1	14/419 (3.3)	3.6	8/521 (1.5)	1.6
eGFR 30 to <45 mL/min/1.73m^2	6/239 (2.5)	2.7	2/138 (1.4)	1.7	5/225 (2.2)	2.4
eGFR <30 mL/min/1.73m^2	0/52	0	0/7	0	0/56	0

(continued)

Table IV. (continued).

AE event	Placebo (N = 3695) n (%) or n/N (%)	Placebo (N = 3695) Rate/100 patient-years	Empagliflozin 10 mg (N = 3806) n (%) or n/N (%)	Empagliflozin 10 mg (N = 3806) Rate/100 patient-years	Empagliflozin 25 mg (N = 4782) n (%) or n/N (%)	Empagliflozin 25 mg (N = 4782) Rate/100 patient-years
Malignancies[¶]	36 (1.0)	1.1	46 (1.2)	1.2	67 (1.4)	1.2
With onset ≥6 months from start of treatment/ patients with exposure ≥6 months	22/2446 (0.9)	1.3	30/2860 (1.0)	1.4	39/3751 (1.0)	1.1
Bladder cancer[‖]	0	NC	2 (0.1)	NC	0	NC
Renal cancer[#]	2 (0.1)	NC	0	NC	1 (<0.1)	NC
Breast cancer[**]	2 (0.1)	NC	1 (<0.1)	NC	1 (<0.1)	NC
Melanoma[††]	1 (<0.1)	NC	2 (0.1)	NC	4 (0.1)	NC
Lung cancer[‡‡]	1 (<0.1)	NC	2 (0.1)	NC	4 (0.1)	NC
AEs consistent with decreased renal function[§§]	36 (1.0)	1.1	46 (1.2)	1.2	64 (1.3)	1.1
Hepatic injury[¶¶]	66 (1.8)	2.0	52 (1.4)	1.4	82 (1.7)	1.5
Diabetic ketoacidosis[‖‖]	5 (0.1)	0.1	2 (0.1)	0.1	1 (<0.1)	<0.1
Venous thromboembolic events[##]	9 (0.2)	0.3	3 (0.1)	0.1	8 (0.2)	0.1

Data from patients who received ≥1 dose of the study drug, including patients who switched to empagliflozin 10 mg or 25 mg in an extension study, unless otherwise indicated.
AE = adverse event; eGFR = estimated glomerular filtration rate by Modification of Diet in Renal Disease equation; MedDRA = Medical Dictionary for Regulatory Activities; NC = not calculated.

[*]Based on 77 MedDRA preferred terms; 23 were reported, of which urinary tract infection, cystitis, and asymptomatic bacteriuria were the most frequent.
[†]Based on 89 MedDRA preferred terms; 29 were reported, of which vulvovaginal mycotic infection, balanitis, and vulvovaginal candidiasis were the most frequent.
[‡]Based on 8 MedDRA preferred terms; 6 were reported, of which hypotension, syncope, and orthostatic hypotension were the most frequent.
[§]Based on 60 MedDRA preferred terms; 31 were reported, of which traumatic fracture, foot fracture, and tooth fracture were the most frequent.
[¶]Based on 2 standardized MedDRA queries.
[‖]Bladder cancer/bladder neoplasm.
[#]Renal cancer/renal cell carcinoma.
[**]Breast cancer/invasive ductal breast cancer.
[††]Malignant melanoma/malignant melanoma in situ.
[‡‡]Lung neoplasm malignant/lung cancer metastatic/non–small cell lung cancer/squamous cell carcinoma of lung.
[§§]Based on 1 standardized MedDRA query.
[¶¶]Based on 4 standardized MedDRA queries.
[‖‖]Based on 3 MedDRA preferred terms.
[##]Based on 5 MedDRA preferred terms.

was higher in female than male patients in all treatment groups, and was higher with empagliflozin than with placebo in male and female patients (Table IV). Events consistent with genital infection were mild or moderate in 99% of patients who experienced them and led to premature treatment discontinuation in a small proportion of patients (<0.1%, 0.4%, and 0.5% in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively). The proportion of patients with events consistent with genital infection that required or prolonged hospitalization was similar in the placebo and empagliflozin groups (0.1%, 0.1%, and <0.1% in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively). The percentage of patients with events consistent with genital infection was greater with empagliflozin than with placebo in patients with a history of chronic or recurrent genital infection (7.8%, 17.1%, and 20.5% in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively) and in patients without such a history (1.0%, 4.4%, and 5.5%, respectively).

Volume Depletion

The incidence of events consistent with volume depletion was similar with empagliflozin and placebo (1.6, 1.5, and 1.3/100 patient-years for the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively). The incidence of these events was similar between empagliflozin and placebo within age subgroups, except for a higher incidence with empagliflozin 25 mg than placebo or empagliflozin 10 mg in patients aged >75 years (4.4 versus 2.3 and 2.5/100 patient-years, respectively). The incidence of events consistent with volume depletion was similar between empagliflozin and placebo regardless of use of diuretics at baseline, but in patients who received loop diuretics at baseline, the incidence was 3.2, 5.6, and 3.4/100 patient-years with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively.

Malignancies

The incidence of malignancies was similar in the placebo (1.1/100 patient-years) and empagliflozin groups (1.2/100 patient-years in both dose groups). The incidence of malignancies with an onset >6 months from the start of treatment was similar in the placebo and empagliflozin groups (1.3, 1.4, and 1.1/100 patient-years in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively), with no apparent difference in the incidence of any specific type of cancer between empagliflozin and placebo (Table IV).

Renal Laboratory Parameters and Renal AEs

Small increases were found in serum creatinine and small decreases in eGFR in all 3 treatment groups, with larger changes in the empagliflozin groups than in the placebo group (Table V). Of note, in a dedicated renal safety profile study in patients with T2DM and stage 2 to 4 CKD, decreases in eGFR observed with empagliflozin over 52 weeks of treatment returned to baseline values after a 3-week post-treatment follow-up period (Figure).[15] The incidence of events consistent with decreased renal function was similar in the placebo and empagliflozin groups (1.1, 1.2, and 1.1/100 patient-years for the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively).

Serum uric acid decreased in patients treated with empagliflozin versus a small increase in the placebo group (Table V). No increase was found in the incidence of nephrolithiasis with empagliflozin versus placebo (1.0, 0.5, and 0.5/100 patient-years in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively) or in the incidence of gout with empagliflozin versus placebo (0.7, 0.5, and 0.4/100 patient-years in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively).

Hepatic Laboratory Parameters and AEs

No clinically relevant changes were found in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, or total bilirubin in any treatment group (Table V). Elevations in liver enzymes to ≥3 times ULN were rare in all treatment groups (Table VI). Greater proportions of patients had ALT and/or AST ≥5 times ULN and ALT and/or AST ≥3 times ULN with bilirubin ≥2 times ULN with empagliflozin than with placebo (Table VI), but these elevations were explained by viral infections or the effects of concomitant medication. No cases met Hy's Law criteria. The incidence of events consistent with hepatic injury was similar in the placebo and empagliflozin groups (2.0, 1.4, and 1.5/100 patient-years in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively).

Table V. Laboratory results.

	Placebo		Empagliflozin 10 mg		Empagliflozin 25 mg	
	Baseline	Change from baseline*	Baseline	Change from baseline*	Baseline	Change from baseline*
Hematocrit, %	41.5 (5.4)	−0.1 (3.6)	41.7 (5.3)	3.4 (4.1)	41.7 (5.3)	3.6 (4.2)
Hemoglobin, g/L	136 (15)	−1 (9)	137 (14)	7 (10)	137 (14)	7 (10)
Uric acid, µmol/L	330.1 (138.6)	3.0 (86.8)	315.8 (127.9)	−32.7 (92.8)	323.6 (131.5)	−36.3 (95.2)
Serum creatinine, µmol/L	89.3 (24.8)	0.9 (13.3)	85.7 (17.7)	1.8 (10.6)	86.6 (23.0)	1.8 (13.3)
eGFR, mL/min/1.73m^2	77.6 (22.6)	−0.5 (11.4)	80.1 (21.5)	−0.9 (11.7)	79.5 (22.3)	−1.0 (12.1)
Aspartate aminotransferase, U/L	15 (13)	0 (12)	15 (11)	−1 (14)	15 (12)	−1 (33)
Alanine aminotransferase, U/L	21 (15)	−1 (13)	20 (14)	−3 (16)	21 (15)	−3 (31)
Alkaline phosphatase, U/L	67 (32)	1 (34)	67 (32)	0 (17)	68 (33)	1 (20)
Total bilirubin, µmol/L	9.0 (3.3)	−0.1 (2.3)	8.9 (3.1)	0.1 (2.5)	9.0 (3.1)	0.1 (4.8)
25-Hydroxy vitamin D, nmol/L	75.4 (35.7)	2.6 (40.0)	77.9 (33.7)	3.1 (34.8)	84.4 (41.2)	4.1 (38.1)
Urinary N-telopeptide (nmol/L)/ creatinine (mmol/L) ratio	41 (24)	−2 (17)	40 (20)	3 (19)	34 (23)	4 (24)
Parathyroid hormone, ng/L	42.3 (19.3)	−3.0 (15.7)	42.2 (18.1)	0.4 (15.0)	36.9 (35.5)	−1.2 (31.0)
Electrolytes						
Sodium, mmol/L	141 (2)	0 (2)	141 (2)	0 (2)	141 (2)	0 (2)
Potassium, mmol/L	4.2 (0.3)	0.0 (0.3)	4.2 (0.3)	0.0 (0.3)	4.2 (0.3)	0.0 (0.3)
Calcium, mmol/L	2.5 (0.1)	0.0 (0.1)	2.4 (0.1)	0.0 (0.1)	2.5 (0.1)	0.0 (0.1)
Magnesium, mmol/L	0.9 (0.1)	0.0 (0.1)	0.9 (0.1)	0.1 (0.1)	0.9 (0.1)	0.1 (0.1)
Phosphate, mmol/L	1.2 (0.1)	0.0 (0.1)	1.2 (0.1)	0.0 (0.1)	1.2 (0.1)	0.0 (0.1)
Total cholesterol, mmol/L	4.5 (1.2)	0.1 (0.8)	4.5 (1.2)	0.1 (0.9)	4.5 (1.1)	0.2 (0.9)
HDL-cholesterol, mmol/L	1.2 (0.3)	0.0 (0.2)	1.2 (0.3)	0.0 (0.2)	1.2 (0.3)	0.1 (0.2)
LDL-cholesterol, mmol/L	2.4 (1.0)	0.1 (0.7)	2.4 (1.0)	0.1 (0.8)	2.4 (0.9)	0.1 (0.7)
LDL-cholesterol/HDL-cholesterol ratio	2.1 (1.0)	0.1 (0.8)	2.1 (0.9)	0.0 (0.7)	2.1 (0.9)	0.0 (0.7)
Triglycerides, mmol/L	1.9 (1.4)	0.1 (1.3)	1.9 (1.7)	0.0 (1.6)	1.9 (1.5)	0.0 (1.2)
Apolipoprotein A-I, g/L	1.26 (0.06)	0.00 (0.04)	1.26 (0.06)	0.01 (0.04)	1.26 (0.06)	0.01 (0.05)
Apolipoprotein B, g/L	0.95 (0.53)	0.07 (0.38)	0.95 (0.53)	0.08 (0.41)	0.96 (0.51)	0.11 (0.38)

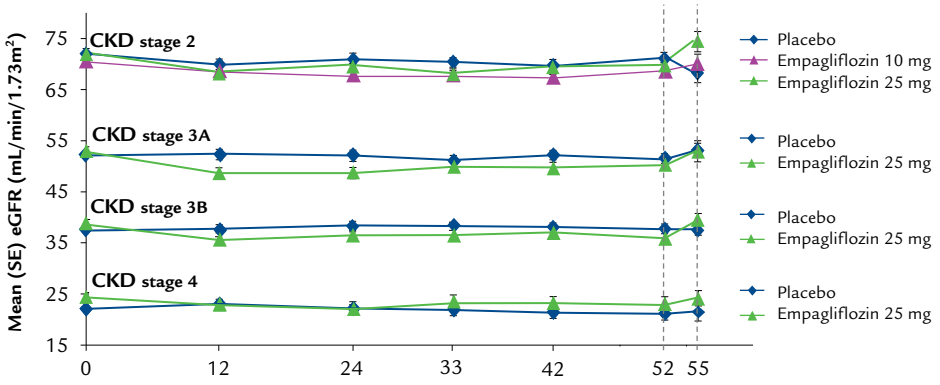
Data are mean (SD) in patients who received ≥1 dose of the study drug, excluding patients who switched to empagliflozin 10 mg or 25 mg in an extension study. Data are normalized to a standard reference range, except for eGFR and lipids.
eGFR = estimated glomerular filtration rate by Modification of Diet in Renal Disease equation;
HDL = high-density lipoprotein; LDL = low-density lipoprotein
*Changes from baseline at last value on treatment.

Hematocrit and Venous Thromboembolic Events

Hemoglobin and hematocrit increased in patients treated with empagliflozin, with almost no change in the placebo group (Table V). The incidence of venous thromboembolic events was low in all groups (0.3, 0.1, and 0.1/100 patient-years in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively).

Electrolytes, Parathyroid Hormone, and Bone Fractures

No meaningful changes were found in serum electrolytes (sodium, potassium, calcium, magnesium, and phosphate), alkaline phosphatase, 25-hydroxy vitamin D, urinary N-telopeptide (NTx)/creatinine ratio, or parathyroid hormone in any treatment group (Table V). The incidence of bone fractures was similar in the placebo and empagliflozin groups (2.1, 1.7, and



Patients analyzed								
CKD stage 2	Placebo	87	86	87	86	86	86	32
	Empa 10mg	90	89	90	89	90	86	39
	Empa 25mg	89	88	88	89	88	89	43
CKD stage 3A	Placebo	79	78	77	75	78	79	44
	Empa 25 mg	82	82	82	82	82	82	45
CKD stage 3B	Placebo	87	86	87	87	87	85	62
	Empa 25 mg	82	80	82	82	81	80	56
CKD stage 4	Placebo	25	25	25	25	25	25	15
	Empa 25 mg	26	26	25	26	26	25	17

Descriptive statistics. eGFR is according to the Modification of Diet in Renal Disease equation. CKD stage 2 = eGFR ≥60 and <90 mL/min/1.73m^2; CKD stage 3A = eGFR ≥45 to <60 mL/min/1.73m^2; CKD stage 3B = eGFR ≥30 to <45 mL/min/1.73m^2; CKD stage 4 = eGFR ≥15 to <30 mL/min/1.73m^2

Figure. Estimated glomerular filtration rate (eGFR) over time, including after treatment follow-up period (dotted lines) in patients with chronic kidney disease (CKD). Empa = empagliflozin.

1.1/100 patient-years for the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively). No imbalance was found in the incidence of bone fractures between empagliflozin and placebo within renal function (eGFR) subgroups (Table IV).

Lipid Parameters

Increases in LDL-cholesterol and total cholesterol were observed in all treatment groups, including the placebo group. A small increase from baseline was found in HDL-cholesterol with empagliflozin 25 mg.

Table VI. Elevations in liver enzymes and bilirubin.

	Placebo (n = 3695)	Empagliflozin 10 mg (n = 3806)	Empagliflozin 25 mg (n = 4782)
ALT and/or AST ≥3 times ULN	37 (1.0)	21 (0.6)	31 (0.6)
ALT and/or AST ≥5 times ULN	3 (0.1)	7 (0.2)	12 (0.3)
ALT and/or AST ≥3 times ULN with bilirubin ≥2 times ULN	0	2 (0.1)	3 (0.1)

Data are n (%) in patients who received ≥1 dose of the study drug, including patients who switched to empagliflozin 10 mg or 25 mg in an extension study.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Table VII. Urine ketone amounts: worst recorded measurement on treatment.

	Placebo (n = 3275)	Empagliflozin 10 mg (n = 3090)	Empagliflozin 25 mg (n = 3998)
Negative	2870 (87.6)	2518 (81.5)	3249 (81.3)
Trace	293 (8.9)	337 (10.9)	416 (10.4)
1+	96 (2.9)	174 (5.6)	249 (6.2)
≥2+	16 (0.5)	61 (2.0)	84 (2.1)

Data are n (%) in patients who received ≥1 dose of the study drug, including patients who switched to empagliflozin 10 mg or 25 mg in an extension study.

No changes in LDL-cholesterol/HDL-cholesterol ratio or triglycerides were observed with empagliflozin 10 mg or 25 mg (Table V). Almost no change in apolipoprotein A-I was found in any treatment group (Table V). Increases in apolipoprotein B were similar between placebo and empagliflozin 10 mg, but were slightly greater with empagliflozin 25 mg (Table V).

DKA

Greater proportions of patients on empagliflozin had urine ketone amounts ≥1+ compared with placebo (Table VII), but the proportions of patients with DKA was similar between groups. DKA was reported in 5 (0.1%), 2 (0.1%), and 1 (<0.1%) patients in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively. The incidence of DKA was 0.12, 0.05, and 0.02/100 patient-years in the placebo, empagliflozin 10 mg, and empagliflozin 25 mg groups, respectively. DKA was reported in 2 male patients and 1 female patient treated with empagliflozin. Two of the patients were on insulin. One patient had a UTI as a precipitating factor. One patient was diagnosed with DKA on the basis of positive urine ketone bodies without acidosis. All patients recovered, and 2 patients continued treatment with empagliflozin.

DISCUSSION

This comprehensive analysis of the safety profile data pooled from Phase I to III clinical trials of empagliflozin which involved >13,000 patients with T2DM was undertaken to establish the safety profile and tolerability of empagliflozin. The total incidences of AEs, severe AEs, serious AEs, and AEs leading to drug discontinuation were not increased in patients treated with empagliflozin compared with placebo.

Empagliflozin was not associated with an increased risk of hypoglycemia compared with placebo, except when used in combination with sulfonylurea and/or basal insulin. Empagliflozin monotherapy would not be expected to be associated with an increased risk of hypoglycemia on the basis of its mode of action, which is independent of the action of insulin.[2] However, sulfonylureas are associated with an increased risk of hypoglycemia, and an increase in hypoglycemia was reported when other antidiabetes medications, including other SGLT2 inhibitors,[27,28] glucagon-like peptide-1 agonists,[29] and dipeptidyl peptidase-4 inhibitors,[30] are used in combination with a sulfonylurea. Consideration should be given to reducing the dose of sulfonylurea to reduce the risk of hypoglycemia when a sulfonylurea is used with empagliflozin.[31] A reduction in insulin dose should be considered when insulin is used in combination with empagliflozin to reduce the risk of hypoglycemia.[31]

SGLT2 inhibitors are associated with osmotic diuresis because of increased loss of glucose in the urine.[2] The potential for volume depletion in vulnerable patients such as the elderly, patients with renal impairment, patients with low systolic blood pressure, and patients receiving diuretics is acknowledged in the prescribing information for empagliflozin.[31] In this large data set, the overall incidence of events consistent with volume depletion was similar with empagliflozin and placebo, but a higher incidence of events consistent with volume depletion was observed in patients aged ≥75 years and in patients who receiving loop diuretics at baseline. AEs of pollakiuria were reported more frequently in patients treated with empagliflozin than with placebo.

The incidence of events consistent with genital infection was higher in patients treated with empagliflozin than with placebo, but such events rarely required or prolonged hospitalization. An increased risk of genital infections, particularly in female patients, has also been observed with other SGLT2 inhibitors.[32,33] In this pooled analysis, the incidence of events consistent with UTI was similar in patients treated with empagliflozin and placebo, but an increased risk of events consistent with UTI, particularly in female patients, has been observed in some trials and is acknowledged in the product label.[31] Few events consistent with UTI required or prolonged hospitalization.

Empagliflozin increases afferent arteriolar glomerular resistance without an alteration in efferent arteriolar resistance, leading to a reduction in glomerular hyperfiltration.[34,35] Thus, the reductions in eGFR observed with empagliflozin are likely to be hemodynamic in nature, and Phase III studies have found that they are reversible after treatment discontinuation.[7,15,17,18] Of note, in this large data set, there was no increase in the incidence of events consistent with decreased renal function with empagliflozin compared with placebo.

Imbalances in bladder and breast cancer were observed with another SGLT2 inhibitor, but analyses were based on short exposure times and small numbers.[36] In this pooled data set, the incidence of malignancies was similar between placebo and empagliflozin. Importantly, the incidence was similar for malignancies with an onset >6 months after the start of treatment, before which a causal link is unlikely, and no differences were found in the incidence of any specific type of cancer between empagliflozin and placebo.

SGLT2 inhibition results in a negative energy balance because of loss of glucose in the urine, leading to a decreased insulin-to-glucagon ratio.[37] As a consequence, SGLT2 inhibition may lead to an increase in fasting amounts of ketone bodies in patients with T2DM.[38] In this large data set, although increased urine ketone amounts were reported in a greater proportion of patients on empagliflozin than on placebo, the incidence of DKA was low and no higher with empagliflozin than with placebo.

Increases in HDL-cholesterol and LDL-cholesterol were observed in some trials of SGLT2 inhibitors,[39] which may be partly due to hemoconcentration effects.[40] However, in this pooled analysis, changes in serum lipids were similar in the empagliflozin and placebo groups. Changes in LDL-cholesterol and apolipoprotein B were small and proportional and suggested that LDL particle size did not change.

It was hypothesized that changes in renal sodium and glucose reabsorption by SGLT2 inhibition may affect bone metabolism through modulation of the renal reabsorption of calcium and phosphate,[41] and an increased risk of bone fracture is listed as a side effect of another SGLT2 inhibitor.[42] However, in this pooled analysis, no increase in bone fractures was found in patients treated with empagliflozin compared with placebo, including patients with stage 2 to 4 CKD.

The glucose transporter (GLUT) 9 in the proximal tubule transports uric acid and glucose.[43] SGLT2 inhibition is believed to lead to an increased efflux of uric acid into the urine as a result of an increased glucose concentration in the proximal tubule, which stimulates GLUT9-mediated uric acid excretion and inhibits GLUT9-mediated uric acid reabsorption.[44] Consistent with this and the results of individual studies, decreases in serum uric acid were observed in patients treated with empagliflozin in this pooled analysis, and no increase was found in the incidence of nephrolithiasis with empagliflozin compared with placebo.

Strengths of this analysis include the large sample size and that it was prespecified. Limitations of this pooled analysis are that the studies included were of varying durations and that differences between groups were not compared with modeled analyses. In addition, it is possible that rare AEs may not be captured in the exposure time of this analysis; therefore, postmarketing surveillance will be important to identify rare AEs.

CONCLUSIONS

In conclusion, in this predefined analysis of pooled data that was based on >9000 patient-years' exposure to empagliflozin, empagliflozin 10 and 25 mg were well tolerated in patients with T2DM. Compared with placebo, the reported frequency of events consistent with UTI, bone fractures, malignancies, decreased renal function, or DKA was not increased with empagliflozin 10 or 25 mg in the presented data. Empagliflozin was not associated with a higher rate of hypoglycemic events compared with placebo, except in patients on background sulfonylurea and/or insulin. The incidence of events consistent with genital infection was higher with empagliflozin than with placebo. The incidence of AEs consistent with volume depletion was similar between empagliflozin and placebo but

was higher with empagliflozin 25 mg in patients aged >75 years.

ACKNOWLEDGMENTS

The studies that provided data for this analysis were funded by the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance. Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Melanie Stephens and Wendy Morris of Fleishman-Hillard Group, Ltd, during the preparation of this manuscript. All authors contributed to the interpretation of data, reviewed and edited the manuscript, were fully responsible for all content and editorial decisions, and have approved the final version.

CONFLICTS OF INTEREST

All the authors are employees of Boehringer Ingelheim. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

REFERENCES

1. Grempler R, Thomas L, Eckhardt M, et al. Empagliflozin, a novel selective sodium glucose cotransporter-2 (SGLT-2) inhibitor: characterisation and comparison with other SGLT-2 inhibitors. *Diabetes Obes Metab*. 2012;14:83–90.
2. Gallo LA, Wright EM, Vallon V. Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. *Diab Vasc Dis Res*. 2015;12:78–89.
3. Haering HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care*. 2013;36:3396–3404.
4. Roden M, Weng J, Eilbracht J, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol*. 2013;1:208–219.
5. Haering HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care*. 2014;37:1650–1659.
6. Kovacs CS, Seshiah V, Swallow R, et al. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. *Diabetes Obes Metab*. 2014;16:147–158.
7. Rosenstock J, Jelaska A, Frappin G, et al. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. *Diabetes Care*. 2014;37:1815–1823.
8. Tikkanen I, Narko K, Zeller C, et al. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. *Diabetes Care*. 2015;38:420–428.
9. Rosenstock J, Jelaska A, Zeller C, et al. Impact of empagliflozin added-on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2015;17:936–948.
10. FDA guidance: reviewer guidance conducting a clinical safety review of a new product application and preparing a report on the review. February 2005. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072974.pdf. Last accessed March 23, 2015.
11. Ferrannini E, Seman L, Seewaldt-Becker E, et al. A Phase IIb, randomized, placebo-controlled study of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes. *Diabetes Obes Metab*. 2013;15:721–728.
12. Heise T, Seman L, Macha S, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising doses of empagliflozin in patients with type 2 diabetes mellitus. *Diabetes Ther*. 2013;4:331–345.
13. Heise T, Seewaldt-Becker E, Macha S, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics following 4 weeks' treatment with empagliflozin once daily in patients with type 2 diabetes. *Diabetes Obes Metab*. 2013;15:613–621.
14. Kanada S, Koiwai K, Taniguchi A, et al. Pharmacokinetics, pharmacodynamics, safety and tolerability of 4 weeks' treatment with empagliflozin in Japanese patients with type 2 diabetes mellitus. *J Diabetes Investig*. 2013;4:613–617.
15. Rosenstock J, Seman LJ, Jelaska A, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. *Diabetes Obes Metab*. 2013;15:1154–1160.
16. Barnett AH, Mithal A, Manassie J, et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2014;2:369–384.
17. Kadowaki T, Haneda M, Inagaki N, et al. Empagliflozin monotherapy in Japanese patients with type 2 diabetes mellitus: a randomized, 12-week, double-blind, placebo-controlled, phase II trial. *Adv Ther*. 2014;31:621–638.
18. Ridderstråle M, Andersen KR, Zeller C, et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. *Lancet Diabetes Endocrinol*. 2014;2:691–700.
19. Zhao X, Cui Y, Zhao S, et al. Pharmacokinetics and pharmacodynamic properties and tolerability of single- and

multiple-dose once-daily empagliflozin, a sodium glucose cotransporter 2 inhibitor, in Chinese patients with type 2 diabetes. *Clin Ther*. 2015;37:1493–1502.
20. Ferrannini E, Berk A, Hantel S, et al. Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: an active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. *Diabetes Care*. 2013;36:4015–4021.
21. Kadowaki T, Haneda M, Inagaki N, et al. Efficacy and safety of empagliflozin monotherapy for 52 weeks in Japanese patients with type 2 diabetes: a randomized, double-blind, parallel-group study. *Adv Ther*. 2015;32:306–318.
22. Haering HU, Merker L, Christiansen AV, et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2015;110:82–90.
23. Kovacs CS, Seshiah V, Merker L, et al. Empagliflozin as add-on therapy to pioglitazone with or without metformin in patients with type 2 diabetes. *Clin Ther*. 2015;37:1773–1788.
24. Merker L, Haering HU, Christiansen AV, et al. Empagliflozin as add-on to metformin in people with type 2 diabetes. *Diabet Med*. 2015;32:1555–1567.
25. Roden M, Merker L, Christiansen AV, et al. Safety, tolerability and effects on cardiometabolic risk factors of empagliflozin monotherapy in drug-naïve patients with type 2 diabetes: a double-blind extension of a Phase III randomized controlled trial. *Cardiovasc Diabetol*. 2015;14:154.
26. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.
27. Ptaszynska A, Johnsson KM, Parikh SJ, et al. Safety profile of dapagliflozin for type 2 diabetes: pooled analysis of clinical studies for overall safety and rare events. *Drug Saf*. 2014;37:815–829.
28. Yang XP, Lai D, Zhong XY, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes: systematic review and meta-analysis. *Eur J Clin Pharmacol*. 2014;70:1149–1158.
29. Garber AJ. Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability. *Diabetes Care*. 2011;34:S279–S284.
30. Scheen AJ. Safety of dipeptidyl peptidase-4 inhibitors for treating type 2 diabetes. *Expert Opin Drug Saf*. 2015;14:505–524.
31. Boehringer Ingelheim Pharmaceuticals, Inc. Jardiance (empagliflozin) US Prescribing Information; 2014.
32. Johnsson KM, Ptaszynska A, Schmitz B, et al. Vulvovaginitis and balanitis in patients with diabetes treated with dapagliflozin. *J Diabetes Complications*. 2013;27:479–484.
33. Rosiak M, Grzeszczak S, Kosior DA, Postuła M. Emerging treatments in type 2 diabetes: focus on canagliflozin. *Ther Clin Risk Manag*. 2014;10:683–689.
34. Cherney DZ, Perkins BA, Soleymanlou N, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation*. 2014;129:587–597.
35. Skrtić M, Yang GK, Perkins BA, et al. Characterisation of glomerular haemodynamic responses to SGLT2 inhibition in patients with type 1 diabetes and renal hyperfiltration. *Diabetologia*. 2014;57:2599–2602.
36. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med*. 2013;159:262–274.
37. Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Invest*. 2014;124:499–508.
38. Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. *J Clin Endocrinol Metab*. 2015;100:2849–2852.
39. Halimi S, Vergès B. Adverse effects and safety of SGLT-2 inhibitors. *Diabetes Metab*. 2014;40:S28–S34.
40. Lund SS, Sattar N, Salsali A, et al. Potential relevance of changes in haematocrit to changes in lipid parameters with empagliflozin in patients with type 2 diabetes. *Diabetologia*. 2015;58:S360.
41. Blaine J, Chonchol M, Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. *Clin J Am Soc Nephrol*. 2014;10:1257–1272.
42. Janssen Pharmaceuticals Inc. Invokana (canagliflozin) US Prescribing Information; 2014.
43. Doblado M, Moley KH. Facilitative glucose transporter 9, a unique hexose and urate transporter. *Am J Physiol Endocrinol Metab*. 2009;297:E831–E835.
44. Chino Y, Samukawa Y, Sakai S, et al. SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. *Biopharm Drug Dispos*. 2014;35:391–404.

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