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ORIGINAL RESEARCH

Safety and Tolerability of Combinations of Empagliflozin and Linagliptin in Patients with Type 2 Diabetes: Pooled Data from Two Randomized Controlled Trials

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ABSTRACT

Introduction: Two 52-week Phase III studies evaluated the efficacy and safety of once-daily combinations of empagliflozin/linagliptin as monotherapy or add-on to metformin in patients with type 2 diabetes (T2DM). The aim of this analysis was to further assess the safety and tolerability of empagliflozin/linagliptin compared with their individual components in patients with T2DM, using pooled data from these trials.

Methods: A total of 1363 patients were treated with empagliflozin 25 mg/linagliptin 5 mg (n = 273), empagliflozin 10 mg/linagliptin 5 mg (n = 272), empagliflozin 25 mg (n = 276), empagliflozin 10 mg (n = 275), or linagliptin 5 mg (n = 267). Adverse events (AEs) were assessed descriptively in patients who took ≥ 1 dose of study drug.

Results: Total exposure was 251, 255, 256, 249, and 243 patient-years in the empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg, and linagliptin 5 mg groups, respectively. The proportion of patients with ≥ 1 AE was similar across groups (70.4–74.9%). The percentage of patients with confirmed hypoglycemic AEs (plasma glucose ≤ 70 mg/dL and/or requiring assistance) was low in all groups (1.1–2.2%); none required assistance. Events consistent with urinary tract infection were reported in similar percentages of patients in all groups (11.4–13.8%), and in a greater proportion of female than male patients. Events consistent with genital infection were reported in higher percentages of patients on empagliflozin/linagliptin or empagliflozin (4.0–6.5%) than linagliptin 5 mg (2.6%), and in a greater proportion of females than males. The risks of hypersensitivity reactions and events consistent with volume depletion were low across treatment groups.

Conclusion: Empagliflozin/linagliptin as monotherapy or add-on to metformin for 52 weeks was well tolerated in patients with T2DM, with safety profiles similar to individual components, including a low risk of hypoglycemia.

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INTRODUCTION

Metformin is recommended as first-line pharmacotherapy for patients with type 2 diabetes (T2DM) in the American Diabetes Association guidelines [1]. While effective initially, metformin treatment alone often fails to maintain glycemic control as T2DM progresses [2–4], and additional glucose-lowering therapies, such as sodium glucose cotransporter 2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors, are required [1]. Using treatments in combination may be preferred to sequential addition for reasons including simplification of drug dosing regimen, reduced pill burden and increased treatment adherence [5–7].

Inhibition of SGLT2 in patients with T2DM reduces renal glucose reabsorption, thereby increasing urinary glucose excretion, leading to a reduction in plasma glucose levels in an insulin-independent manner [8–10]. Linagliptin reduces blood glucose in patients with T2DM by preventing degradation of incretin peptides such as glucagon-like peptide 1 (GLP-1), stimulating insulin release and inhibiting glucagon secretion [11]. The efficacy and safety of once-daily combinations of empagliflozin/linagliptin as monotherapy or add-on to metformin in patients with T2DM were assessed in two double-blind 52-week Phase III studies. As add-on to metformin, combinations of empagliflozin 10 or 25 mg with linagliptin 5 mg significantly reduced HbA1c versus the individual components [12]. As initial therapy, empagliflozin 10 mg/linagliptin 5 mg significantly reduced HbA1c versus empagliflozin 10 mg or linagliptin 5 mg, and empagliflozin 25 mg/linagliptin 5 mg significantly reduced HbA1c versus linagliptin 5 mg, but reductions in HbA1c were not significant versus empagliflozin 25 mg [13]. In these trials, the safety profiles of empagliflozin/linagliptin were similar to the known safety profiles of the individual components [12, 13]. We used the large pool of data from these two double-blind trials to conduct a detailed analysis of the safety and tolerability of once-daily combinations of empagliflozin/linagliptin compared with their individual components for 52 weeks in patients with T2DM.

METHODS

Patients

Data were pooled from two Phase III, randomized, double-blind, parallel-group studies in patients with T2DM, one that evaluated combinations of empagliflozin/linagliptin as initial therapy (trial registration: ClinicalTrials.gov identifier, NCT01422876) [13], and one that evaluated combinations of empagliflozin/linagliptin as second-line therapy in patients inadequately controlled on metformin (trial registration: ClinicalTrials.gov identifier, NCT01422876) [12]. In both studies, eligible patients were aged $\geq$ 18 years with body mass index (BMI) $\leq$ 45 kg/m^2 and HbA1c $\geq$ 7% to $\leq$ 10.5% at screening. In the initial therapy study, patients who had not received treatment with an oral antidiabetes therapy, GLP-1 analogue, or insulin for $\geq$ 12 weeks were randomized 1:1:1:1:1 to empagliflozin 25 mg/linagliptin 5 mg as a fixed dose combination (FDC) tablet, empagliflozin 10 mg/linagliptin 5 mg as a FDC tablet, empagliflozin 25 mg, empagliflozin 10 mg, or linagliptin 5 mg for 52 weeks [13]. In the add-on to metformin study, patients who were receiving metformin immediate release ($\geq$ 1500 mg/day, maximum tolerated dose, or maximum dose according to local label) at a dose unchanged for $\geq$ 12 weeks were randomized 1:1:1:1:1 to empagliflozin 25 mg/linagliptin 5 mg as an FDC tablet, empagliflozin 10 mg/linagliptin 5 mg FDC tablet, empagliflozin 25 mg, empagliflozin 10 mg, or linagliptin 5 mg for 52 weeks as add-on to metformin at an unchanged dose [12]. FDC tablets, empagliflozin tablets and linagliptin tablets were taken once daily in the morning. The studies were conducted in 197 centers in 22 countries. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the

Declaration of Helsinki in accordance with the International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice. An independent ethics committee or institutional review board approved the clinical protocol at each participating center. All participants gave signed and dated informed consent prior to inclusion.

Assessments and Data Analyses

Safety and tolerability over 52 weeks was assessed via reporting of adverse events (AEs) and laboratory parameters. AEs assessed were those reported by investigators, coded according to preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0. The assessment of AEs was based on events that occurred during treatment or within 7 days after the last dose of the study drug. AEs classified as serious were as reported by the investigator. A mild AE was defined as an awareness of signs or symptoms which are easily tolerated, as judged by the investigator. A moderate AE was defined as an AE judged by the investigator to create enough discomfort to cause interference with usual activity. A severe AE was defined as an AE judged by the investigator 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 significant disability/incapacity, required or prolonged patient hospitalization, was a congenital anomaly/birth defect, or was deemed serious for any other reason based on appropriate medical judgment. AEs of interest included confirmed hypoglycemic AEs (plasma glucose $\leq$ 70 mg/dL and/or requiring assistance), events consistent with urinary tract infection (UTI), genital infection, and volume depletion, hypersensitivity reactions, pancreatitis and cancer. Assessment of laboratory parameters included changes from baseline in hematocrit, electrolytes, lipids, estimated glomerular filtration rate (eGFR; according to the Modification of Diet in Renal Disease equation) and uric acid. Analyses were descriptive and based on patients who received $\geq$ 1 dose of study drug.

RESULTS

Patient Disposition, Exposure and Baseline Characteristics

A total of 1363 patients received $\geq$ 1 dose of study drug, 677 as initial therapy and 686 as add-on to metformin. Total exposures were 251, 255, 256, 249, and 243 patient-years in the empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg, and linagliptin 5 mg groups, respectively. Baseline demographics and clinical characteristics were similar among the five treatment groups (Table 1).

Summary of Adverse Events

The proportion of patients with $\geq$ 1 AE was similar across treatment groups (Table 2). Most events were mild or moderate in intensity; severe events were reported in 7.0% of patients on empagliflozin 25 mg/linagliptin 5 mg, 6.3% on empagliflozin 10 mg/linagliptin 5 mg, 5.1% on empagliflozin 25 mg, 6.2% on empagliflozin 10 mg and 3.4% on linagliptin 5 mg. Serious AEs were reported in 4.4% of patients on empagliflozin 25 mg/linagliptin 5 mg, 5.9% on empagliflozin 10 mg/linagliptin 5 mg, 6.9% on empagliflozin 25 mg, 5.8% on empagliflozin 10 mg and 3.7% on linagliptin. Similar proportions of patients discontinued because of AEs across the treatment groups. There were two deaths in the empagliflozin 10 mg/linagliptin 5 mg group (hypertensive heart disease and hemorrhagic stroke), two deaths in the empagliflozin 25 mg group (meningitis tuberculosis and hepatic mass), and two deaths in the empagliflozin 10 mg group (lung neoplasm/metastatic non-small cell lung cancer and brain edema). The most common AE preferred terms reported were urinary tract infection, headache, upper respiratory tract infection, nasopharyngitis, hyperglycemia and arthralgia (Table 2). No patients experienced worsening of heart failure or were hospitalized due to heart failure. There were no cases of lower limb amputation in any treatment group.

Table 1 Baseline characteristics

	Empagliflozin 25 mg/linagliptin 5 mg (n = 273)	Empagliflozin 10 mg/linagliptin 5 mg (n = 272)	Empagliflozin 25 mg (n = 276)	Empagliflozin 10 mg (n = 275)	Linagliptin 5 mg (n = 267)
Male	145 (53.1)	158 (58.1)	144 (52.2)	146 (53.1)	142 (53.2)
Age, years	55.7 (10.2)	55.7 (10.0)	55.6 (9.8)	54.9 (10.5)	55.0 (10.8)
Race					
White	205 (75.1)	204 (75.0)	194 (70.3)	209 (76.0)	201 (75.3)
Asian	34 (12.5)	32 (11.8)	40 (14.5)	32 (11.6)	32 (12.0)
Black/African American	17 (6.2)	24 (8.8)	24 (8.7)	17 (6.2)	17 (6.4)
Other	17 (6.2)	12 (4.4)	18 (6.5)	17 (6.2)	17 (6.4)
Time since diagnosis of type 2 diabetes, years					
≤ 1	53 (19.4)	65 (23.9)	58 (21.0)	57 (20.7)	60 (22.5)
> 1–5	101 (37.0)	97 (35.7)	100 (36.2)	114 (41.5)	106 (39.7)
> 5–10	75 (27.5)	73 (26.8)	75 (27.2)	55 (20.0)	65 (24.3)
> 10	44 (16.1)	37 (13.6)	43 (15.6)	49 (17.8)	36 (13.5)
HbA1c, %	7.94 (0.87)	8.01 (0.89)	8.01 (0.90)	8.01 (0.98)	8.03 (0.89)
Weight, kg	86.8 (19.4)	86.9 (18.7)	87.2 (18.6)	86.8 (21.2)	87.4 (19.7)
Body mass index, kg/m^2	31.3 (5.5)	31.1 (5.6)	31.5 (5.5)	31.2 (5.5)	31.2 (5.8)
Systolic blood pressure, mmHg	129.7 (15.2)	128.9 (14.7)	129.1 (14.0)	130.1 (15.1)	128.0 (13.9)
Diastolic blood pressure, mmHg	78.4 (9.1)	78.7 (8.4)	79.3 (8.9)	79.7 (9.1)	78.0 (8.8)
Estimated glomerular filtration rate (MDRD), mL/min/1.73 m^2	88.9 (18.8)	88.5 (17.9)	89.5 (18.4)	89.8 (19.4)	89.7 (20.1)

Data are number of patients (%) or mean (SD) in patients treated with $\geq$ 1 dose of study drug
MDRD Modification of Diet in Renal Disease equation

Hypoglycemia

The proportion of patients with confirmed hypoglycemic AEs was low and similar in all treatment groups (1.8%, 1.1%, 2.2%, 2.2% and 1.5% of patients on empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg and linagliptin 5 mg, respectively; Table 3). No patients experienced confirmed hypoglycemic AEs that required assistance and no patients discontinued due to hypoglycemia.

Urinary Tract Infection

Events consistent with UTI were reported in a similar proportion of patients in each treatment group (11.4–13.8%) (Table 3). Notably, there was no increase in events consistent with UTI in any of the four empagliflozin treatment groups

Table 2 Summary of number of patients with AEs

	Empagliflozin 25 mg/linagliptin 5 mg (n = 273)	Empagliflozin 10 mg/linagliptin 5 mg (n = 272)	Empagliflozin 25 mg (n = 276)	Empagliflozin 10 mg (n = 275)	Linagliptin 5 mg (n = 267)
One or more AE(s)	201 (73.6)	193 (71.0)	196 (71.0)	206 (74.9)	188 (70.4)
Most common AEs[a]					
Urinary tract infection	27 (9.9)	29 (10.7)	25 (9.1)	30 (10.9)	27 (10.1)
Headache	16 (5.9)	15 (5.5)	13 (4.7)	19 (6.9)	24 (9.0)
Upper respiratory tract infection	19 (7.0)	19 (7.0)	18 (6.5)	13 (4.7)	16 (6.0)
Nasopharyngitis	18 (6.6)	16 (5.9)	10 (3.6)	16 (5.8)	20 (7.5)
Hyperglycemia	8 (2.9)	8 (2.9)	12 (4.3)	13 (4.7)	24 (9.0)
Arthralgia	5 (1.8)	14 (5.1)	13 (4.7)	10 (3.6)	12 (4.5)
One or more drug-related[b] AE(s)	41 (15.0)	37 (13.6)	48 (17.4)	42 (15.3)	32 (12.0)
One or more AE(s) leading to treatment discontinuation	12 (4.4)	10 (3.7)	9 (3.3)	16 (5.8)	6 (2.2)
One or more severe AE(s)	19 (7.0)	17 (6.3)	14 (5.1)	17 (6.2)	9 (3.4)
One or more serious AE(s)	12 (4.4)	16 (5.9)	19 (6.9)	16 (5.8)	10 (3.7)
Deaths	0	2 (0.7)	2 (0.7)	2 (0.7)	0

Data are number of patients (%) with $\geq$ 1 event in patients treated with $\geq$ 1 dose of study drug

[a] Preferred terms reported in $\geq$ 5% of patients in any treatment group

[b] As defined by the investigator

compared with the linagliptin group. Of patients who experienced an event consistent with UTI, most experienced only one event (71.0%, 79.4%, 66.7%, 89.5%, and 82.4% of patients on empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg and linagliptin 5 mg, respectively). A greater proportion of female than male patients in each group experienced an event consistent with UTI. Of patients who experienced events consistent with UTI, their worst reported episodes were mild in 80.6%, 76.5%, 60.6%, 78.9% and 85.3% of patients on empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg and linagliptin 5 mg, respectively, and reported events were moderate in 19.4%, 23.5%, 36.4%, 18.4% and 11.8% of patients on empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg and linagliptin 5 mg, respectively. Events consistent with UTI led to discontinuation in two patients on empagliflozin 10 mg. Events consistent with UTI that required or prolonged hospitalization were reported in 1.1%, 0.4% and 0.4% of patients in empagliflozin 25 mg, empagliflozin

Table 3 Number of patients with AEs of interest

	Empagliflozin 25 mg/ linagliptin 5 mg (*n* = 273)	**Empagliflozin 10 mg/linagliptin 5 mg (*n* = 272)**	**Empagliflozin 25 mg (*n* = 276)**	**Empagliflozin 10 mg (*n* = 275)**	**Linagliptin 5 mg (*n* = 267)**
Confirmed hypoglycemic AEs[a]	5 (1.8)	3 (1.1)	6 (2.2)	6 (2.2)	4 (1.5)
Events requiring assistance	0	0	0	0	0
Events consistent with urinary tract infection[b]	31 (11.4)	34 (12.5)	33 (12.0)	38 (13.8)	34 (12.7)
Female	25 (19.5)	27 (23.7)	28 (21.2)	29 (22.5)	29 (23.2)
Male	6 (4.1)	7 (4.4)	5 (3.5)	9 (6.2)	5 (3.5)
Events consistent with genital infection[c]	11 (4.0)	12 (4.4)	18 (6.5)	18 (6.5)	7 (2.6)
Female	4 (3.1)	9 (7.9)	14 (10.6)	11 (8.5)	4 (3.2)
Male	7 (4.8)	3 (1.9)	4 (2.8)	7 (4.8)	3 (2.1)
Events consistent with volume depletion[d]	2 (0.7)	5 (1.8)	2 (0.7)	1 (0.4)	4 (1.5)
Dehydration	1 (0.4)	1 (0.4)	1 (0.4)	0	2 (0.7)
Hypotension	1 (0.4)	2 (0.7)	0	1 (0.4)	2 (0.7)
Syncope	0	2 (0.7)	2 (0.7)	0	0
Orthostatic hypotension	0	0	0	0	1 (0.4)
Hypersensitivity reactions[e]	3 (1.1)	2 (0.7)	2 (0.7)	2 (0.7)	1 (0.4)
Asthma	0	1 (0.4)	0	2 (0.7)	0
Urticaria	0	1 (0.4)	2 (0.7)	0	0
Angiodema	1 (0.4)	0	0	0	1 (0.4)
Asthmatic crisis	1 (0.4)	0	0	0	0
Eyelid edema	1 (0.4)	0	0	0	0
Pancreatitis[f]	1 (0.4)	0	0	0	1 (0.4)
Acute pancreatitis	1 (0.4)	0	0	0	0
Chronic pancreatitis	0	0	0	0	1 (0.4)

Table 3 continued

	Empagliflozin 25 mg/ linagliptin 5 mg (n = 273)	Empagliflozin 10 mg/linagliptin 5 mg (n = 272)	Empagliflozin 25 mg (n = 276)	Empagliflozin 10 mg (n = 275)	Linagliptin 5 mg (n = 267)
Decreased renal function[g]	1 (0.4)	0	0	0	1 (0.4)
Acute renal failure	0	0	0	0	1 (0.4)
Renal impairment	1 (0.4)	0	0	0	0
Cancer events	5 (1.8)	2 (0.7)	2 (0.7)	2 (0.7)	2 (0.7)
Adenoid cystic carcinoma	0	0	0	1 (0.4)	0
Basal cell carcinoma	1 (0.4)	0	1 (0.4)	0	0
Breast cancer	1 (0.4)	0	0	0	0
Renal cancer[h]	2 (0.7)	0	0	0	0
Gastrointestinal carcinoma	0	1 (0.4)	0	0	0
Lung cancer[i]	0	1 (0.4)	0	1 (0.4)	0
Metastases to peritoneum	0	0	1 (0.4)	0	0
Ovarian cancer	0	0	1 (0.4)	0	0
Prostate cancer[j]	1 (0.4)	0	0	0	1 (0.4)
Squamous cell carcinoma	0	0	0	0	1 (0.4)

Data are number of patients (%) with $\geq$ 1 event in patients treated with $\geq$ 1 dose of study drug
SMQ standardized, *MedDRA query* Medical Dictionary for Regulatory Activities
[a] Plasma glucose $\leq$ 70 mg/dL and/or requiring assistance
[b] Based on 70 preferred terms
[c] Based on 89 preferred terms
[d] Based on 8 preferred terms
[e] Based on 3 SMQs
[f] Based on 1 SMQ and 1 preferred term
[g] Based on 1 SMQ
[h] Based on preferred terms: clear cell renal cell carcinoma/renal cancer
[i] Based on preferred terms: lung adenocarcinoma/lung neoplasm/non-small cell lung cancer metastatic
[j] Based on preferred terms: prostate cancer/prostatic specific antigen increased

10 mg, and linagliptin 5 mg groups, respectively, and none in the combination therapy groups. Acute pyelonephritis was reported in one patient who was on linagliptin 5 mg: the event was severe in intensity and was considered to be related to the study drug. Chronic pyelonephritis was reported in two patients: one patient on empagliflozin 10 mg experienced chronic pyelonephritis that was mild in intensity and was not considered to be related to study drug; one patient on empagliflozin 25 mg experienced moderate exacerbation of

chronic pyelonephritis that did not lead to discontinuation of the study drug.

Genital Infection

Events consistent with genital infection were reported in 4.0% of patients on empagliflozin 25 mg/linagliptin 5 mg, 4.4% on empagliflozin 10 mg/linagliptin 5 mg, 6.5% on empagliflozin 25 mg, 6.5% on empagliflozin 10 mg and 2.6% on linagliptin 5 mg (Table 3). Of patients who experienced an event consistent with genital infection, most experienced only one event (81.8%, 83.3%, 66.7%, 77.8% and 85.7% of patients on empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg and linagliptin 5 mg, respectively). Events consistent with genital infection were reported in a greater proportion of female than male patients in all groups except empagliflozin 25 mg/linagliptin 5 mg (Table 3). Of patients who experienced events consistent with genital infection, reported events were mild in 54.5%, 83.3%, 61.1%, 72.2% and 57.1% of patients on empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg and linagliptin 5 mg, respectively, and reported events were moderate in 45.5%, 16.7%, 38.9%, 22.2% and 42.9% of patients on empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, empagliflozin 25 mg, empagliflozin 10 mg and linagliptin 5 mg, respectively. Events consistent with genital infection led to discontinuation in one patient on empagliflozin 25 mg/linagliptin 5 mg, two patients on empagliflozin 25 mg and one on empagliflozin 10 mg. No patients experienced genital infections that required or prolonged hospitalization.

Volume Depletion

Events consistent with volume depletion were reported in two patients on empagliflozin 25 mg/linagliptin 5 mg (dehydration and hypotension), five on empagliflozin 10 mg/linagliptin 5 mg (dehydration, hypotension, and syncope), two on empagliflozin 25 mg (dehydration and syncope), one on empagliflozin 10 mg (hypotension) and four on linagliptin 5 mg (dehydration, hypotension, and orthostatic hypotension) (Table 3). Serious events consistent with volume depletion were reported in one patient on empagliflozin 10 mg/linagliptin 5 mg (hypotension), two on empagliflozin 25 mg (dehydration and syncope) and two on linagliptin 5 mg (dehydration and hypotension).

Hypersensitivity Reactions, Pancreatitis and Diabetic Ketoacidosis

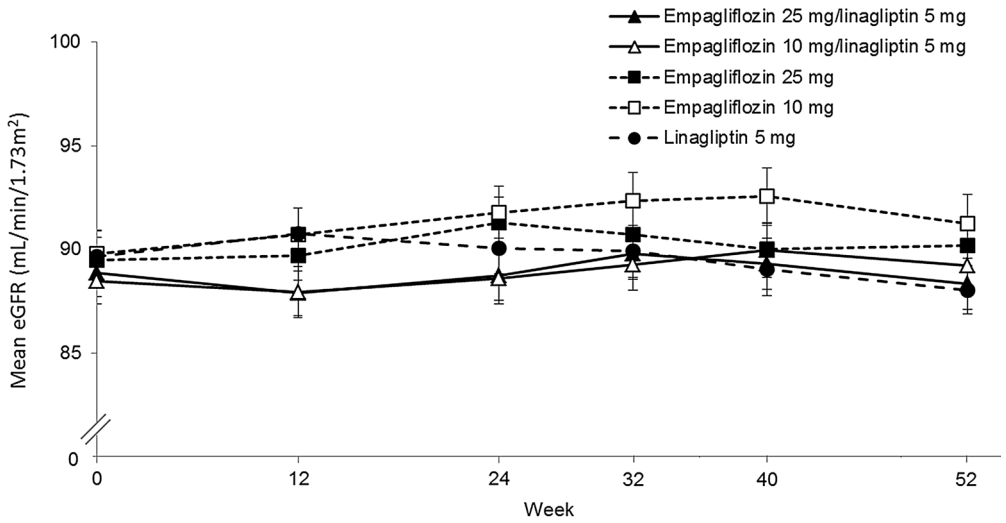
Hypersensitivity reactions were reported in three patients on empagliflozin 25 mg/linagliptin 5 mg (angioedema, asthmatic crisis, and eyelid edema), two on empagliflozin 10 mg/linagliptin 5 mg (asthma and urticaria), two on empagliflozin 25 mg (urticaria), two on empagliflozin 10 mg (asthma) and one on linagliptin 5 mg (angiodema) (Table 3). Acute pancreatitis was reported in one patient on empagliflozin 25 mg/linagliptin 5 mg (Table 3). Chronic pancreatitis was reported in one patient on linagliptin 5 mg after approximately 11 months of treatment; the investigator did not consider the pancreatitis to be related to the study medication and did not discontinue or reduce the study medication. No diabetic ketoacidosis AEs were reported.

Renal Adverse Events and Laboratory Parameters

Changes from baseline in eGFR were generally small and similar in all treatment groups (Fig. 1). Decreased renal function AEs were reported in one patient on empagliflozin 25 mg/linagliptin 5 mg (renal impairment) and one patient on linagliptin 5 mg (acute renal failure) (Table 3).

Cancer

Cancer events were reported in five patients on empagliflozin 25 mg/linagliptin 5 mg and two patients in each of the other groups (Table 3).



Number of subjects						
Empagliflozin 25 mg/linagliptin 5 mg	273	263	248	241	240	231
Empagliflozin 10 mg/linagliptin 5 mg	272	266	255	251	244	240
Empagliflozin 25 mg	276	267	255	248	245	237
Empagliflozin 10 mg	275	258	249	237	239	224
Linagliptin 5 mg	267	255	239	236	234	227

Fig. 1 Estimated glomerular filtration rate (eGFR; according to Modification of Diet in Renal Disease formula) over 52 weeks. Descriptive statistics in patients treated with ≥ 1 dose of study drug. Data are mean ± SE

Different types of cancer were reported in each group.

Lipid Laboratory Parameters

There were small increases from baseline in total cholesterol in the empagliflozin/linagliptin and the empagliflozin groups, and a small decrease in the linagliptin 5 mg group (Table 4). There were small increases from baseline in HDL-cholesterol in all treatment groups. No consistent pattern was observed in changes from baseline in LDL-cholesterol; there were small decreases with empagliflozin 10 mg/linagliptin 5 mg and linagliptin 5 mg, and small increases in the other groups (Table 4). There was a decrease in triglycerides in the empagliflozin 25 mg and linagliptin 5 mg groups (Table 4).

Other Laboratory Parameters

Mean changes from baseline in hematocrit were + 4.3 to + 4.9% in the empagliflozin/linagliptin and empagliflozin groups and + 1.3% in the linagliptin group (Table 4). Mean changes from baseline in uric acid were − 0.9 to − 1.1 mg/dL in the empagliflozin/linagliptin and empagliflozin groups and + 0.1 mg/dL in the linagliptin group (Table 4). There were no clinically meaningful changes in electrolytes (Table 4).

DISCUSSION

This analysis of pooled safety data from two 52-week Phase III trials was undertaken to further characterize the safety and tolerability of once daily empagliflozin/linagliptin compared with its individual components in patients with T2DM. Empagliflozin/linagliptin as monotherapy or add-on to metformin for 52 weeks were well tolerated, with safety profiles similar to the individual components. Most AEs were mild or moderate in intensity, and the proportion of patients with AEs leading to discontinuation was similar across treatment groups. Slightly higher percentages of patients had severe or

Table 4 Clinical laboratory parameters

	Empagliflozin 25 mg/linagliptin 5 mg (n = 263)[a]		Empagliflozin 10 mg/linagliptin 5 mg (n = 267)[b]		Empagliflozin 25 mg (n = 268)[c]		Empagliflozin 10 mg (n = 261)[d]		Linagliptin 5 mg (n = 255)[e]	
	Baseline	Change from baseline	Baseline	Change from baseline	Baseline	Change from baseline	Baseline	Change from baseline	Baseline	Change from baseline
Hematocrit, %	42.2 (4.8)	4.9 (3.8)	42.4 (5.0)	4.6 (3.8)	42.5 (5.2)	4.7 (3.9)	42.9 (4.9)	4.3 (3.6)	42.3 (5.3)	1.3 (3.8)
Uric acid, mg/dL	4.9 (1.9)	− 1.0 (1.4)	5.3 (1.9)	− 1.1 (1.4)	5.2 (2.0)	− 1.1 (1.6)	5.1 (2.0)	− 0.9 (1.4)	5.0 (2.0)	0.1 (1.2)
Creatinine, mg/dL	0.9 (0.1)	0.0 (0.1)	0.9 (0.1)	0.0 (0.1)	0.9 (0.1)	− 0.0 (0.1)	0.9 (0.1)	− 0.0 (0.1)	0.9 (0.1)	0.0 (0.1)
Electrolytes										
Sodium, mEq/L	141 (2)	1 (2)	141 (2)	1 (2)	141 (2)	1 (2)	141 (2)	1 (2)	141 (2)	0 (2)
Potassium, mEq/L	4.1 (0.3)	0.1 (0.3)	4.1 (0.3)	0.0 (0.3)	4.1 (0.3)	0.0 (0.3)	4.2 (0.3)	0.1 (0.4)	4.1 (0.3)	0.1 (0.3)
Calcium, mg/dL	9.7 (0.4)	− 0.0 (0.4)	9.7 (0.4)	− 0.0 (0.4)	9.7 (0.4)	− 0.0 (0.5)	9.8 (0.4)	− 0.1 (0.5)	9.7 (0.4)	− 0.1 (0.5)
Magnesium, mEq/L	1.8 (0.2)	0.1 (0.1)	1.8 (0.2)	0.1 (0.2)	1.8 (0.2)	0.1 (0.1)	1.8 (0.2)	0.1 (0.1)	1.8 (0.2)	0.0 (0.2)
Phosphate, mg/dL	3.7 (0.2)	0.1 (0.2)	3.7 (0.2)	0.0 (0.2)	3.7 (0.2)	0.1 (0.3)	3.7 (0.2)	0.1 (0.3)	3.7 (0.2)	0.0 (0.2)
Total cholesterol, mg/dL	176.6 (60.3)	8.6 (46.7)	178.0 (63.8)	4.4 (54.5)	182.1 (62.2)	8.3 (52.8)	186.4 (61.2)	6.6 (45.2)	184.8 (76.3)	− 2.9 (61.5)
HDL-cholesterol, mg/dL	43.1 (6.2)	1.9 (3.4)	42.0 (5.4)	1.9 (3.5)	43.0 (6.6)	2.3 (3.9)	42.6 (6.0)	1.8 (3.6)	42.5 (5.5)	0.7 (3.3)
LDL-cholesterol, mg/dL	80.9 (27.8)	1.9 (21.9)	82.2 (30.5)	− 0.2 (26.5)	81.6 (26.5)	2.3 (22.8)	83.8 (27.1)	0.8 (21.7)	83.8 (30.3)	− 1.6 (22.5)

Table 4 continued

	Empagliflozin 25 mg/ linagliptin 5 mg (n = 263)[a]		Empagliflozin 10 mg/ linagliptin 5 mg (n = 267)[b]		Empagliflozin 25 mg (n = 268)[c]		Empagliflozin 10 mg (n = 261)[d]		Linagliptin 5 mg (n = 255)[e]	
	Baseline	Change from baseline	Baseline	Change from baseline	Baseline	Change from baseline	Baseline	Change from baseline	Baseline	Change from baseline
Triglycerides, mg/dL	103.5 (63.4)	− 1.0 (45.5)	108.3 (61.9)	0.8 (51.6)	116.2 (95.5)	− 7.5 (76.1)	119.3 (80.1)	0.5 (57.7)	114.5 (147.9)	− 4.7 (110.0)

Data are mean (SD) in patients treated with ≥ 1 dose of study drug. Changes from baseline are based on last values on treatment. Data are normalized to a standard reference range

HDL high-density lipoprotein, *LDL* low-density lipoprotein

[a] n = 255 for lipid parameters

[b] n = 266 for potassium, calcium and magnesium; n = 260 for lipid parameters

[c] n = 267 for hematocrit; n = 269 for lipid parameters

[d] n = 258 for hematocrit; n = 254 for lipid parameters

[e] n = 254 for hematocrit and lipid parameters

serious AEs with empagliflozin/linagliptin or empagliflozin compared with linagliptin.

Hypoglycemia is the major limiting factor in the glycemic management of T2DM [1]. The risk of hypoglycemia associated with each drug should be considered when choosing second- and third-line therapy [1]. Empagliflozin and linagliptin are associated with a low risk of hypoglycemia when given as monotherapy [14, 15] or as add-on to metformin [16–21]. Therefore, combination therapy with empagliflozin and linagliptin would not be expected to be associated with an increased risk of hypoglycemia. Further, the mechanism of action of empagliflozin is insulin-independent, and although linagliptin causes stimulation of insulin secretion and inhibition of glucagon secretion, these effects are glucose-dependent [9, 11]. In this pooled analysis of > 1300 patients receiving empagliflozin/linagliptin or individual components as monotherapy or add-on to metformin, the proportion of patients with confirmed hypoglycemic AEs was low and similar across treatment groups, and no hypoglycemic AEs requiring assistance were reported.

In this pooled analysis, the proportion of patients with events consistent with UTI was similar in all groups. The proportion of patients with events consistent with genital infection was higher in patients on empagliflozin/linagliptin or empagliflozin than linagliptin, but no such events required or prolonged hospitalization. Most events consistent with UTI or genital infection were mild in intensity. Events consistent with UTI were reported in a greater proportion of females than males. Events consistent with genital infection were reported in a greater proportion of females than males except in the empagliflozin 25 mg/linagliptin 5 mg group. This observation in the empagliflozin 25 mg/linagliptin 5 mg group may be due to the low number of events. These findings are consistent with an analysis of pooled safety data from Phase I–III trials of empagliflozin in patients with T2DM in which the incidence of events consistent with UTI was not increased with empagliflozin but events consistent with genital infection occurred more frequently in participants treated with empagliflozin than placebo [22]. The risk of UTI or genital infections is not increased with linagliptin [15]. An increased risk of events consistent with UTI or genital infection is acknowledged in the product labels for empagliflozin [23] and empagliflozin/linagliptin [24].

Treatment with empagliflozin leads to osmotic diuresis [25, 26], which may lead to intravascular volume contraction and adverse reactions related to volume depletion or dehydration. 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 [23] and empagliflozin/linagliptin [24]. In this pooled analysis, the risk of volume depletion (including dehydration) was low and similar between groups.

There have been post-marketing reports of serious hypersensitivity reactions and acute pancreatitis, including fatal pancreatitis, in patients treated with linagliptin [27]; this is acknowledged in the product labels for linagliptin [27] and empagliflozin/linagliptin [24]. In this pooled analysis, the risk of hypersensitivity reactions and pancreatitis was low across treatment groups.

In this pooled analysis, small changes in eGFR were observed in all treatment groups. Decreased renal function AEs were reported in only two patients. Changes from baseline in total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides with empagliflozin/linagliptin were small and in line with those observed with empagliflozin in a large pooled analysis of safety data [22]. There were no clinically relevant changes in electrolytes in the present pooled analysis.

The strengths of this analysis are the large number of patients assessed and the 52-week duration of treatment. Limitations include the lack of a placebo arm in either of the studies.

CONCLUSION

In this pooled analysis of > 1300 patients with T2DM, empagliflozin/linagliptin as monotherapy or add-on to metformin for 52 weeks was

well tolerated, with safety profiles similar to individual components, including a low risk of hypoglycemia.

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Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki in accordance with the International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice. An independent ethics committee or institutional review board approved the clinical protocol at each participating center. All participants gave signed and dated informed consent prior to inclusion.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes—2018. Diabetes Care. 2018;41(Suppl. 1):S1–159.

2. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA. 1999;281:2005–12.

3. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006;355:2427–43.

4. Fonseca VA. Defining and characterizing the progression of type 2 diabetes. Diabetes Care. 2009;32(Suppl 2):S151–6.

5. DeFronzo RA. Banting lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58:773–95.

6. Hutchins V, Zhang B, Fleurence RL, et al. A systematic review of adherence, treatment satisfaction and costs, in fixed-dose combination regimens in type 2 diabetes. Curr Med Res Opin. 2011;27:1157–68.

7. Woo V. Empagliflozin/linagliptin single-tablet combination: first-in-class treatment option. Int J Clin Pract. 2015;69:1427–37.

8. Abdul-Ghani MA, Norton L, DeFronzo RA. Renal sodium-glucose cotransporter inhibition in the management of type 2 diabetes mellitus. Am J Physiol Renal Physiol. 2015;309:F889–900.

9. 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.

10. DeFronzo RA, Norton L, Abdul-Ghani M. Renal, metabolic and cardiovascular considerations of SGLT2 inhibition. Nat Rev Nephrol. 2017;13:11–26.

11. Gallwitz B. Emerging DPP-4 inhibitors: focus on linagliptin for type 2 diabetes. Diabetes Metab Syndr Obes. 2013;6:1–9.

12. DeFronzo R, Lewin A, Patel S, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care. 2015;38:384–93.

13. Lewin A, DeFronzo R, Patel S, et al. Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes. Diabetes Care. 2015;38:394–402.

14. 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;1:208–19.

15. Gomis R, Owens DR, Taskinen MR, et al. Long-term safety and efficacy of linagliptin as monotherapy or in combination with other oral glucose-lowering agents in 2121 subjects with type 2 diabetes: up to 2 years exposure in 24-week phase III trials followed by a 78-week open-label extension. Int J Clin Pract. 2012;66:731–40.

16. Häring H-U, 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;37:1650–9.

17. Merker L, Haering HU, Christiansen AV, et al. Empagliflozin as add-on to metformin in people with type 2 diabetes. Diabet Med. 2015;32:1555–67.

18. Taskinen MR, Rosenstock J, Tamminen I, et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab. 2011;13:65–74.

19. Schernthaner G, Barnett AH, Emser A, et al. Safety and tolerability of linagliptin: a pooled analysis of data from randomized controlled trials in 3572 patients with type 2 diabetes mellitus. Diabetes Obes Metab. 2012;14:470–8.

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;36:4015–21.

21. Lehrke M, Marx N, Patel S, et al. Safety and tolerability of linagliptin in patients with type 2 diabetes: a comprehensive pooled analysis of 22 placebo-controlled studies. Clin Ther. 2014;36:1130–45.

22. Kohler S, Zeller C, Iliev H, Kaspers S. Safety and tolerability of empagliflozin in patients with type 2 diabetes: pooled analysis of Phase I–III clinical trials. Adv Ther. 2017;34:1707–26.

23. Boehringer Ingelheim Pharmaceuticals, Inc. Jardiance (empagliflozin) US Prescribing Information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204629s008lbl.pdf.

24. Boehringer Ingelheim Pharmaceuticals, Inc. Glyxambi (empagliflozin and linagliptin) US Prescribing Information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206073s000lbl.pdf.

25. Heise T, Jordan J, Wanner C, et al. Pharmacodynamic effects of single and multiple doses of empagliflozin in patients with type 2 diabetes. Clin Ther. 2016;38:2265–76.

26. Heise T, Jordan J, Wanner C, et al. Acute pharmacodynamic effects of empagliflozin with and without diuretic agents in patients with type 2 diabetes mellitus. Clin Ther. 2016;38:2248–64.

27. Boehringer Ingelheim Pharmaceuticals, Inc. Tradjenta (linagliptin) US Prescribing Information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/201280s005lbl.pdf.