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Safety of Empagliflozin in Patients with Type 2 Diabetes Mellitus in Saudi Arabia: A Post-Authorisation Safety Study

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Abstract

Background: Empagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor is used as a monotherapy or in combination for lowering the elevated blood glucose level in patients with type 2 diabetes mellitus (T2DM). It is often associated with certain adverse reactions (urinary tract infection (UTI), diabetes ketoacidosis (DKA), and genital infections). Thus, the Saudi Food and Drug Administration requested a post-authorisation safety study to monitor the safety of empagliflozin during the defined observation period. ***Methodology***: The local, comparator, non-interventional, regulatory post-marketing study using "new user" design was conducted in patients with T2DM, treated with empagliflozin (10 or 25 mg) and dipeptidyl peptidase-4 (DPP-4) inhibitors (NCT03764631). Study was conducted from 2018 to 2020, wherein each patient was followed up for 12 months after the index period. Incidence and occurrence of DKA, severe UTIs, volume depletion and dehydration were observed along with metformin, insulin and treatment complexity status and adverse events in the index and Ramadan period. All data collected were analysed using descriptive statistics. ***Results***: Among the 1502 patients enrolled (empagliflozin [n = 751] and DPP-4 inhibitors [n = 751]), 0.1% patients (n = 1) in each group and <1% patients (n = 13) (0.8% [n = 6]: empagliflozin group; 0.9% [n = 7]: DPP-4 inhibitor group) reported the incidence of DKA and volume depletion, respectively. No severe UTIs or dehydration was evident in either group in the index period. No patients reported T2DM-associated complications during the Ramadan period. Metformin, insulin, and treatment com-

plexity status were also evaluated during the study. Overall, 8.1% of patients (n = 121) reported adverse events in the index period while only 0.3% of patients (n = 4) reported adverse events during the Ramadan period. Comparable decline in mean glycated haemoglobin, and no major change in vital signs, along with 81.3% of patients (n = 1221) confirming concomitant medications were noted. ***Conclusion***: Empagliflozin was well tolerated over a period of 12 months, with no safety concerns and a favourable benefit/risk ratio.

Keywords

Type 2 Diabetes Mellitus, Diabetes Ketoacidosis, Dehydration, Urinary Tract Infection, Volume Depletion, Ramadan, SGLT2 Inhibitor, Saudi Arabia

1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common chronic metabolic disorders affecting people within the age group of 20 to 79 years, with a global prevalence rate of 9.3% [1] [2]. According to the International Diabetes Federation report, 537 million people are currently living with diabetes worldwide, while 73 million people are affected in the Middle East and North Africa region, with adult prevalence rate in Saudi Arabia being 17.7% [3]. Saudi Arabia has the second-highest prevalence of T2DM in the Middle East and stands seventh in terms of global prevalence. It represents a major public health concern due to associated high levels of morbidity and mortality [4] [5] [6] [7] [8].

Diabetes mellitus is characterised by elevated levels of blood glucose, attributable to the malfunctioning of the feedback loops between insulin action and insulin secretion, thereby culminating into a metabolic imbalance [2]. Pharmacological interventions for T2DM have witnessed a paradigm shift from conventional biguanides (metformin), thiazolidinediones and insulin secretagogues (sulphonylureas and meglitinide analogues) to novel sodium-glucose co-transporter type 2 (SGLT2) inhibitors, incretin mimetics (dipeptidyl peptidase-4 [DPP-4] inhibitors, and glucagon-like peptide 1 receptor agonists) [9] [10] [11]. However, the cornerstone of T2DM management is lifestyle modification, exercise, cessation of smoking, healthy diet and weight management [12].

An important drug category for T2DM used in the recent past is SGLT2 inhibitors that act by diminishing the blood glucose level via partial blockage of glucose reabsorption from the kidney back to the bloodstream, thereby improving the diabetes control [1]. It is also evident that SGLT2 inhibitors improve the renal and cardiovascular outcomes [13]. Several studies have reported that SGLT2 inhibitors are well tolerated and exhibit dose-dependent effectiveness, particularly empagliflozin [1] [14] [15] [16] [17] [18]. Empagliflozin is being widely used as a monotherapy or as an add-on combination therapy; however, it is associated with certain adverse events (AEs) such as urinary tract infection (UTI), diabetic ke-

toacidosis (DKA) and hypoglycaemia [17] [19] [20] [21]. Based on its safety and effectiveness profile, the use of empagliflozin could be paramount during the Ramadan period as this period showcases the aggravation of several risk factors in patients with T2DM, including hypoglycaemia, hyperglycaemia, DKA, dehydration and thrombosis [10] [22].

Therefore, parallel to the launch of SGLT2 inhibitors in Saudi Arabia, post-authorisation safety study (PASS) was conducted upon the request of Saudi Food and Drug Authority (SFDA) to monitor the safety aspects of empagliflozin in patients with T2DM.

2. Patients and Methods

2.1. Study Design and Participant Selection

This local, comparator, non-interventional, regulatory post-marketing study was conducted to monitor the safety of empagliflozin in patients with T2DM. "New users" design was used wherein comparison was made between empagliflozin (10 or 25 mg) versus DPP-4 inhibitors. A total of 25 sites participated in the study, of which only 18 sites enrolled a total of 1502 patients. The details of the study sites have been incorporated in supplementary **Table S1**. The study was conducted from 2018 to 2020; each patient was followed up for 12 months after the index period, inclusive of Ramadan period. The inclusion criteria for patients in both groups, namely empagliflozin and DPP-4 inhibitors, were primary diagnosis of T2DM performed in Saudi Arabia, having signed informed consent form, at least 18 years of age at the index period, not used other SGLT2 or DPP-4 inhibitors during the previous 12 months of the index period. The exclusion criteria included known hypersensitivity or contraindication to empagliflozin or DPP-4 inhibitor, or any other excipient and the patient being prescribed fixed dose combination (FDC) of SGLT2 inhibitors with DPP-4 inhibitors.

Index period was defined as the date on which each identified new user received the index prescription for empagliflozin or DPP-4 inhibitor.

Ramadan period was defined as the first day of Ramadan to 29th day of Ramadan based on the Islamic Hijri calendar; for 2019: 05 May to 04 Jun. 2019 (±1 to 2 days); for 2020: 23 Apr to 23 May 2020 (±1 to 2 days).

2.2. Ethical Considerations

The ethics committee approval was obtained from the Medical Services General Directorate, Research and Ethics Committee, Western Region, Saudi Arabia for 23 sites out of 25 (IRB Registration No. H-02-T-078). One site was approved by IRB, King Fahad Medical Centre (IRB Registration No. H-01-R-012) while another site was approved by Research Center, International Medical Center (IRB Registration No. 2018-12-102). The study was conducted in accordance with the Declaration of Helsinki. The patients signed the informed consent form before enrolling in the study. The study was conducted in accordance with the laws, regulations, and relevant guidelines of Saudi Arabia. (NCT03764631)

2.3. Methodology

All patients were followed up for 12 months after the index period (inclusive of Ramadan period) or until any of the specified conditions were met (death, specific exclusion criteria, the last continuous treatment of the index drug [empagliflozin or DPP-4 inhibitor], or new treatment episode started with any of the other index drugs). All the patients attended 4 follow-up visits at baseline, Week 16 ± 2, Week 32 ± 2 and Week 52. The investigators assessed and recorded the preliminary study parameters such as medical history, glycated haemoglobin (HbA1c), blood glucose level, renal functions, physical examinations, concomitant mediations, comorbidities, prior medication exposure, AEs, hospitalisation, etc. at successive visits, wherever applicable, into the electronic case report forms.

The incidence and time of first occurrence of DKA, severe UTI, volume depletion and dehydration were the primary outcomes and were evaluated in the index period (Diabetes ketoacidosis is defined as a serious complication of diabetes characterised by high level of ketones in the body due to lack of insulin and low food intake; severe UTI is defined as pyelonephritis or urosepsis; volume depletion is defined as the reduction in the extracellular fluids; and dehydration is defined as the loss of total body water that leads to hypertonicity). The secondary outcomes were diabetes-associated complications evaluated during the Ramadan period. Metformin, insulin, and treatment complexity status, along with analysis of AEs were conducted across both the treatment groups at the index and follow-up period along with Ramadan period.

2.4. Analysis

The sample size of 1500 patients was planned as per the SFDA requirements; as per regulations to detect DKA, 750 patients need to be enrolled in each group. Propensity scores were used for the quantitative analysis of probability of receiving empagliflozin at the index date for new users of both empagliflozin and DPP-4 inhibitors. Sensitivity analysis was performed to evaluate potential bias and confounding. The data collected were represented as arithmetic means, standard deviations (SDs), medians, minimum and maximum values for continuous data and confidence intervals (CI), wherever applicable. All statistical tests were conducted with a 2-sided significance level α of 0.05 and analysis was performed using statistical analysis software (SAS®) version 9.4.

3. Results

3.1. Study Population

Overall, 1502 patients were enrolled in the study, of which 93.7% (n = 1408) completed 1 year of treatment and their treatment status was still ongoing at the end of study. Of the remaining patients, 5.7% (n = 86) terminated the study early due to loss to follow-up (4.9%, n = 74); switching of treatment (0.4%, n = 6); AE-related termination (0.1%, n = 1); and reasons not specified (0.3%, n = 5). The data were unavailable for 0.5% of patients (n = 8) after completion of 1 year

of treatment.

Overall, 64.2% (n = 965) of the enrolled patients were male and the mean age of the enrolled patients at index date was 52.5 ± 10.5 years (Table 1). The overall median duration of T2DM at index period was 53 months and more than 60% (n = 982) of the patients had a family history of T2DM. The most common medical condition across both the groups was metabolism and nutritional disorders (36.6%, n = 550), followed by vascular disorders (20.3%, n = 305) (with respect to System Organ Class [SOC]), while hypertension (20%, n = 301) followed by hyperlipidaemia (14.6%, n = 220) and dyslipidaemia (11.9%, n = 178) were the primary conditions as per the preferred term [PT]). More than 90% of the patients reported no prior insulin use. The mean HbA1c, fasting blood glucose (FBG), complete blood count (CBC), liver function tests, renal function parameters and lipid profile were comparable across the 2 treatment groups. Majority of the patients (81.3%, n = 1221) were on prior medications, with 77.8% (n = 1168) being on anti-hyperglycaemic agents and 19.5% on lipid-modifying agents (19.5%, n = 293).

3.2. Primary Outcomes

Only 0.1% (n = 1) of patient in both the treatment groups reported the occurrence of DKA; the first occurrence in the index period in the empagliflozin and the DPP-4 inhibitor groups was 365 days and 344 days, respectively. However, 0.8% (n = 6) patients in the empagliflozin group and 0.9% (n = 7) patients in the DPP-4 inhibitor group (total: <1%, n = 13) exhibited the occurrence of volume depletion; the time to first occurrence in the index period in empagliflozin and DPP-4 inhibitor groups was 169 ± 131 days and 256.1 ± 110.5 days, respectively. The treatment-adjusted incidence rate ratio of DKA and volume depletion in empagliflozin/DPP-4 inhibitors groups was 0.981 and 0.841, respectively (Table 2). None of the patients reported the occurrence of UTI and dehydration across both treatment groups. Similar result was observed in the follow-up period.

3.3. Secondary Outcomes

None of the patients in the 2 treatment groups had the incidence of DKA, severe UTI, volume depletion or dehydration in the index and follow-up periods during Ramadan.

3.4. Metformin Status at Baseline

Out of 751 patients in each treatment group, 271 patients in the empagliflozin group and 331 patients in the DPP-4 inhibitors group were on metformin FDC therapy at baseline. The occurrence of DKA in those on metformin was reported by 0.4% and 0.3% (n = 1 in each case) of patients in the empagliflozin and DPP-4 inhibitor groups, respectively. Out of the 13 patients (<1%) reporting volume depletion, 1.1% (n = 3) were on empagliflozin and 1.2% (n = 4) were on DPP-4 inhibitor; metformin was used as FDC in both cases at baseline (Table 3). None of the patients on metformin FDC at baseline reported the incidence of

DKA in the index period. No patients across both the treatment groups reported the incidence of severe UTI or dehydration in the index period. Similar results were obtained during the follow-up period.

Table 1. Patient demographics.

Parameter	Empagliflozin (N = 751)	DPP-4 Inhibitors (N = 751)	Total (N = 1502)
Age at index date (years)			
Mean	52.1	52.9	52.5
SD	10.3	10.7	10.5
Median	52	53	52.5
Minimum	21	21	21
Maximum	80	92	92
<30	6 (0.8)	5 (0.7)	11 (0.7)
30 to 64	663 (88.3)	645 (85.9)	1308 (87.1)
>64	82 (10.9)	101 (13.4)	183 (12.2)
Gender, n (%)			
Male	478 (63.6)	486 (64.8)	965 (64.2)
Female	273 (36.4)	264 (35.2)	537 (35.8)

Abbreviation: DPP-4: Dipeptidyl peptidase-4.

Table 2. Incidence of diabetic ketoacidosis and volume depletion in the index period.

Parameters	Empagliflozin (N = 751)	DPP-4 Inhibitors (N = 751)	Rate Ratio
Incidence of DKA			
Patients with events in the period, n (%)	1 (0.1)	1 (0.1)	
Patients without event, n (%)	750 (99.9)	750 (99.9)	
Crude incidence rate	0.001	0.001	1
(95% confidence interval)	0 (0.007)	0 (0.007)	
Treatment-adjusted incidence rate			
(crude per 1000 patient-years)	1.380	1.407	0.981
(95% confidence interval)	(0.035, 7.690)	(0.036, 7.842)	
Incidence of volume depletion			
Patients with events in the period, n (%)	6 (0.8)	7 (0.9)	
Patients without event, n (%)	745 (99.2)	744 (99.1)	
Crude incidence rate	0.008	0.009	0.889
(95% confidence interval)	(0.003, 0.017)	(0.004, 0.019)	
Treatment-adjusted incidence rate			
(crude per 1000 patient-years)	8.282	9.852	0.841
(95% confidence interval)	(3.04, 18.03)	(3.96, 20.30)	

Abbreviation: DKA: Diabetic ketoacidosis; DPP-4: Dipeptidyl peptidase-4. Note: The mean ± SD duration of the index period and follow-up period was 350.6 ± 66.7 days and 351 ± 65.7 days, respectively. Crude incidence rate is the proportion of patients with events in the respective period.

Table 3. Incidence of diabetic ketoacidosis and volume depletion in index period by metformin status.

Parameters	Empagliflozin (N = 271)	DPP-4 Inhibitors (N = 331)	Rate Ratio
Incidence of DKA with metformin			
Patients with events in the period, n (%)	1 (0.4)	1 (0.3)	
Crude incidence rate	0.004	0.003	1.333
(95% confidence interval)	(0, 0.020)	(0, 0.017)	
Treatment-adjusted incidence rate			
(crude per 1000 patient-years)	1.380	1.407	0.981
(95% confidence interval)	(0.035, 7.690)	(0.036, 7.842)	
Incidence of volume depletion with metformin			
Patients with events in the period, n (%)	3 (1.1)	4 (1.2)	
Patients without event, n (%)	268 (98.9)	327 (98.8)	
Crude incidence rate	0.011	0.012	0.917
(95% confidence interval)	(0.002, 0.032)	(0.003, 0.031)	
Treatment-adjusted incidence rate			
(crude per 1000 patient-years)	4.141	5.630	0.736
(95% confidence interval)	(0.854, 12.101)	(1.534, 14.415)	
Time from start of period to first occurrence in period (days)	76.7 ± 15	225 ± 137.9	
	Empagliflozin (N = 480)	**DPP-4 Inhibitors (N = 420)**	**Rate Ratio**
Incidence of volume depletion without metformin			
Patients with events in the period, n (%)	3 (0.6)	3 (0.7)	
Patients without event, n (%)	477 (99.4)	417 (99.3)	
Crude incidence rate	0.006	0.007	0.857
(95% confidence interval)	(0.001, 0.018)	(0.001, 0.021)	
Treatment-adjusted incidence rate			
(crude per 1000 patient-years)	4.141	4.222	0.981
(95% confidence interval)	(0.854, 12.101)	(0.871, 12.340)	
Time from start of period to first occurrence in period (days)	261.3 ± 130.8	297.7 ± 60	

Abbreviation: DKA: Diabetic ketoacidosis; DPP-4: Dipeptidyl peptidase-4.

None of the patients across both treatment groups had the incidence of DKA, UTI, volume depletion and dehydration in the index and follow-up periods during Ramadan.

3.5. Treatment Complexity Status at Baseline

The patients in each treatment group were divided based on the treatment complexity status: on mono glucose-lowering drug (GLD) treatment (empagliflozin group: 116 patients; DPP-4 inhibitor group: 113 patients), dual GLD treatment (empagliflozin group: 343 patients; DPP-4 inhibitor group: 393 patients), triple

GLD treatment (empagliflozin group: 231 patients; DPP-4 inhibitor group: 209 patients), quadruple GLD treatment (empagliflozin group: 43 patients; DPP-4 inhibitor group: 29 patients), quintuple GLD treatment (empagliflozin group: 12 patients; DPP-4 inhibitor group: 6 patients), sextuple GLD treatment (empagliflozin group: 4 patients; DPP-4 inhibitor group: 1 patients), septuple GLD treatment (empagliflozin group: 1 patient; DPP-4 inhibitor group: 0 patients) and octuple GLD treatment (empagliflozin group: 1 patient; DPP-4 inhibitor group: 0 patients).

It was reported that 2.3% (n = 1) and 0.3% patients (n = 1) reported DKA in the empagliflozin group and DPP-4 inhibitor groups while being on quadruple GLDs and dual GLDs therapy, respectively, at the baseline. All 13 patients (<1%) reporting volume depletion was on GLD combinations at baseline (dual, triple, quadruple, and quintuple (Table 4). None of the patients in either of the 2 treatment groups had the incidence of severe UTI or dehydration in the index period. Similar results were reported in the follow-up period.

None of the patients in 2 treatment groups had the incidence of DKA, severe UTI, volume depletion or dehydration in the index and follow-up periods during Ramadan.

Table 4. Incidence of diabetic ketoacidosis and volume depletion in index period by glucose-lowering drug status.

Incidence of DKA in Index Period by GLD Status—Dual Treatment			
	Empagliflozin (N = 343)	**DPP-4 Inhibitors (N = 393)**	**Rate Ratio**
Patients with events in the period, n(%)	0	1 (0.3)	
Crude incidence rate	0	0.003	0
(95% confidence interval)	(0, 0.011)	(0, 0.014)	
Treatment-adjusted incidence rate			
(crude per 1000 patient-years)	0	1.407	0
(95% confidence interval)	(0, 5.092)	(0.036, 7.842)	
Incidence of DKA in Index Period by GLD Status—Quadruple Treatment			
	Empagliflozin (N = 43)	**DPP-4 Inhibitors (N = 29)**	**Rate Ratio**
Patients with events in the period, n (%)	1 (2.3)	0	
Crude incidence rate	0.023	0	
(95% confidence interval)	(0.001, 0.123)	(0.000, 0.119)	
Treatment-adjusted incidence rate			
(crude per 1000 patient-years)	1.380	0.000	
(95% confidence interval)	(0.035, 7.690)	(0, 5.192)	
Incidence of Volume Depletion in Index Period by GLD Status—Dual Treatment			
	Empagliflozin N = 343	**DPP-4 Inhibitors N = 393**	**Rate Ratio**
Patients with events in the period, n (%)	2 (0.6)	5 (1.3)	
Patients without event, n (%)	341 (99.4)	388 (98.7)	

Continued

Crude incidence rate	0.006	0.013	0.462
(95% confidence interval)	(0.001, 0.021)	(0.004, 0.029)	
Treatment-adjusted incidence rate			
(crude per 1000 patient-years)	2.761	7.037	0.392
(95% confidence interval)	(0.334, 9.972)	(2.285, 16.423)	
Time from start of period to first occurrence in period (days)	229 ± 190.9	287 ± 75.6	

Incidence of Volume Depletion in Index Period by GLD Status—Triple Treatment

	Empagliflozin N = 231	**DPP-4 Inhibitors** N = 209	**Rate Ratio**
Patients with events in the period, n (%)	2 (0.9)	1 (0.5)	
Patients without event, n (%)	229 (99.1)	208 (99.5)	
Crude incidence rate	0.009	0.005	1.800
(95% confidence interval)	(0.001, 0.031)	(0.000, 0.026)	
Treatment-adjusted incidence rate			
(crude per 1000 patient-years)	2.761	1.407	1.962
(95% confidence interval)	(0.334, 9.972)	(0.036, 7.842)	
Time from start of period to first occurrence in period (days)	187 ± 168.3	309	

Incidence of Volume Depletion in Index Period by GLD Status—Quadruple Treatment

	Empagliflozin N = 43	**DPP-4 Inhibitors** N = 29	**Rate Ratio**
Patients with events in the period, n (%)	0	1 (3.4)	
Crude incidence rate	0	0.034	0
(95% confidence interval)	(0, 0.082)	(0.001, 0.178)	
Treatment-adjusted incidence rate			
(crude per 1000 patient-years)	0	1.407	0
(95% confidence interval)	(0, 5.092)	(0.036, 7.842)	

Incidence of Volume Depletion in Index Period by GLD Status—Quintuple Treatment

	Empagliflozin N = 12	**DPP-4 Inhibitors** N = 6	**Rate Ratio**
Patients with events in the period, n (%)	2 (16.7)	0	
Patients without event, n (%)	10 (83.3)	6 (100)	
Crude incidence rate	0.167	0	
(95% confidence interval)	(0.021, 0.484)	(0, 0.459)	
Treatment-adjusted incidence rate			
(crude per 1000 patient-years)	2.761	0	
(95% confidence interval)	(0.334, 9.972)	(0, 5.192)	
Time from start of period to first occurrence in period (days)	91 ± 32.5		

Abbreviation: DKA: Diabetic ketoacidosis; DPP-4: Dipeptidyl peptidase-4; GLD: Glucose-lowering drugs.

3.6. Insulin Use at Baseline

The primary outcomes were evaluated based on the use of insulin at baseline, wherein 50 patients in the empagliflozin group and 26 patients in the DPP-4 inhibitors group confirmed the usage.

The occurrence of DKA was reported in 2% of the patients (n = 1) in the empagliflozin group using insulin and 0.1% (n = 1) of the patient on DPP-4 inhibitor without insulin at baseline. Out of the 13 patients (<1%) reporting volume depletion, only 2% of the patients (n = 1) in the empagliflozin group confirmed the use of insulin (Supplementary Table S2). None of the patients in the 2 treatment groups had the incidence of severe UTI or dehydration in the index period. Similar results were reported in the follow-up period.

None of the patients in the 2 treatment groups had the incidence of DKA, severe UTI, volume depletion or dehydration in the index and follow-up periods during Ramadan.

3.7. Adverse Event Summary

Overall, 8.1% (n = 121) of patients reported AEs, wherein 7.7% of patients (n = 58) were treated with empagliflozin and 8.4% of the patients (n = 63) with DPP-4 inhibitor in the index period. A total of 0.3% of the patients (n = 4) reported AEs in the index period during Ramadan, where 0.4% (n = 3) were from the empagliflozin group and 0.1% (n = 1) was treated with DPP-4 inhibitors. A detailed representation of different types of AEs is provided in Table 5.

Table 5. Classification of different adverse events observed.

	Empagliflozin (N = 751)	DPP-4 Inhibitors (N = 751)	Total (N = 1502)
Number (%) of patients			
with any AE	58 (7.7)	63 (8.4)	121 (8.1)
with any severe AE	2 (0.3)	1 (0.1)	3 (0.2)
with any SAE	6 (0.8)	2 (0.3)	8 (0.5)
with any designated SAE	2 (0.3)	2 (0.3)	4 (0.3)
hospitalised	6 (0.8)	1 (0.1)	7 (0.5)
hospitalised with any AESI	1 (0.1)	1 (0.1)	2 (0.1)
Number (%) of deaths	0	0	0
Number (%) of patients discontinuing study due to AE	0	1 (0.1)	1 (0.1)
Number (%) of patients discontinuing treatment due to AE	1 (0.1)	2 (0.3)	3 (0.2)
In the Index Period during Ramadan			
Number (%) of patients with any AE	3 (0.4)	1 (0.1)	4 (0.3)

Abbreviation: AE: Adverse event; AESI: Adverse event of special interest; DPP-4: Dipeptidyl peptidase-4; SAE: Serious adverse event. Note: The mean ± SD duration of the index period and follow-up period during Ramadan was 30.8 ± 3.0 days.

3.7.1. In Relation to SOC and PT

On further analysis based on the SOC and PT in the index period, maximum events reported were gastrointestinal disorders (26 events), followed by nervous system disorders (23 events) and general disorders and administration (20 events). With respect to PT, none of the AEs were present in >1% of the patients in the 2 treatment groups. In the index period during Ramadan, a total of 0.3% (n = 4) patients reported 4 AEs, where 0.4% (n = 3) of patients in the empagliflozin group reported 3 AEs (infections and infestations [corona virus infection], metabolism and nutrition disorder [hypoglycaemia] and renal and urinary disorder [chromaturia] [1 patient each]) and 0.1% (n = 1) patient in the DPP-4 inhibitors group reported 1 AE (gastrointestinal disorder [nausea]).

3.7.2. Incidence of AEs in Relation to Study Treatment

A total of 8 empagliflozin-related AEs were observed in 1.1% of patients (n = 8) (hypoglycaemia: 3; thirst: 2; fungal infection: 2; genital fungal infection:1). However, most of these events were mild, except for 1 event each of hypoglycaemia and fungal infection. During the Ramadan period, 0.4% (n = 1) patient reported 1 empagliflozin-related hypoglycaemia.

3.7.3. Incidence of Adverse Events of Special Interest

A total of 0.3% of patients (n = 4) reported 5 adverse events of special interest (AESIs) in the index period (empagliflozin group: 0.1% [n = 1] patient each of DKA and UTI; DPP-4 inhibitor group: 0.1% [n = 1] patient reported DKA, 0.1% [n = 1] patient reported 1 event each of acute kidney injury and end-stage renal disease).

3.7.4. Serious Adverse Events

A total of 0.5% (n = 8) of patients reported 10 serious AEs (SAEs) in the index period, where 6 patients were from the empagliflozin group, and 2 patients were from the DPP-4 inhibitor group. Of 6 patients reporting 7 SAEs in the empagliflozin group, 1 patient each reported 1 SAE of myocardial ischaemia, anal fissure, hernia, DKA and obesity, and 1 patient reported 2 SAEs (pneumonia and lung adenocarcinoma). Of the 2 patients treated with DPP-4 inhibitor, 3 SAEs were reported (1 patient reported 1 event of DKA and another patient reported 2 SAEs [acute kidney injury and end-stage renal disease]).

3.8. Other Variables

Comparable decline was reported in mean HbA1c levels from baseline to visits 2, 3 and 4 in both treatment groups. No major changes were observed in mean weight, body mass index, pulse rate, systolic blood pressure and diastolic blood pressure across different visits. A total of 8.3% patients (n = 1221) affirmed using concomitant medication, primarily anti-hyperglycaemic medications (empagliflozin group: 82.8% [n = 622]; DPP-4 inhibitor group: 79.8% [n = 599]), followed by lipid-modifying agents (empagliflozin group: 20.1% [n = 151]; DPP-4 inhibitor group: 20% [n = 150]); and agents acting on renin-angiotensin system (em-

pagliflozin group: 14.2% [n = 105]; DPP-4 inhibitor group: 12.3% [n = 92]). Similar results were reported in the index and follow-up periods during Ramadan.

4. Discussion

Previous clinical studies have established the safety and effectiveness of SGLT2 inhibitors in significantly improving the glycaemic control along with exhibiting a well-tolerated safety profile [1] [14] [23] [24] [25] [26] [27]. The pharmacokinetic and exposure-response studies of empagliflozin substantiated no significant change in the risk of UTI, hypoglycaemia or volume depletion [15] and a well-documented favourable benefit-risk profile was established [28]. Empagliflozin has been incorporated as an add-on to metformin therapy and as monotherapy, it is well tolerated in both cases [19] [21] [29]. However, certain studies have shed light on hypoglycaemic AEs, UTIs and volume depletion across treatment groups using SGLT2 during different studies [21] [30].

The association of T2DM with DKA was established in 41.4% of the patients with T2DM in a hospital-based retrospective analysis, thereby highlighting the risk factor in patients with T2DM [31]. A separate study presented DKA as a major concern in using SGLT2, where hospitalisation was observed in 4 patients, thereby reinforcing the need to establish the safety profile of these medications [32]. It was studied that DKA is prevalent in almost one-third of the patients presenting with T2DM, causing an increase in the hospitalisation and economic burden [33] [34]. In a post-authorisation safety and effectiveness study of dapagliflozin in Saudi Arabia, 12.3% of the patients with T2DM reported the AEs, with UTI and DKA at 1% and 0.2% of all the events, respectively [14]. Another paramount concern in patients with T2DM is UTI that warrants a routine urine analysis. It was established that patients with T2DM more than 40 years of age and female patients in particular are at a higher risk of asymptomatic UTI, although the overall prevalence of UTI in T2DM is nearly 11.5% [35] [36] [37] [38]. A retrospective analysis of tofogliflozin, an SGLT2 inhibitor, exhibited significant glucose-lowering competencies with low associated risk of electrolyte abnormalities and dehydration [39]. Ertugliflozin, an SGLT2 inhibitor, did not lead to significant volume depletion (1.2% - 1.9%; dose-dependent) as reported in the randomised double-blind trial [40]. The key trends observed in the current study using empagliflozin were in corroboration with the previously published clinical evidence, where less than 1% of the patients reported T2DM-associated complications (0.1% patients [n = 1] reported DKA each from empagliflozin and DPP-4 inhibitor group; <1% patients reported volume depletion across both the groups). None of the patients reported UTI or dehydration. Thus, the obtained results reinforced the safety profile of empagliflozin.

The medical ramifications of fasting during Ramadan are still unexplored. However, because of the fasting in patients with T2DM, insulin secretion is perturbed, resulting in T2DM-associated complications such as hypoglycaemia, hyper-

glycaemia, DKA, dehydration and thrombosis along with a significant lowering in the blood lipid profile, blood pressure, HbA1c level [10] [22] [41]. A meta-analysis reported that there was an improvement in the HbA1c and hypoglycaemic control when patients with T2DM were treated with SGLT2 during Ramadan, with no major AEs [42]. The DIA-RAMADAN, a real-world study and VIRTUE study evaluated the safety profile of anti-diabetic treatment during the Ramadan period which reported reductions in HbA1c, weight control and fasting plasma glucose [22] [43]. The outcome of the present study with empagliflozin confirmed that none of the patients reported any incidence of DKA, UTI, volume depletion or dehydration during the Ramadan period, which was in line with the established literature.

Thus, the present study provides insights on the safety aspect of empagliflozin, an SGLT2 inhibitor, which was exhibited to be safe during the 1-year period in Saudi Arabia, parallel to its launch in the region. However, we do acknowledge certain limitations of the study. The incidences of DKA, severe UTI, volume depletion and dehydration were not analysed across different age groups, male versus female, duration of disease and varying doses of study treatment. The sample size was determined as per the SFDA requirement, which could be received as limited considering the anticipated incidences of outcomes. Laboratory investigations (CBC, lipid profile, and liver and renal function tests) were not performed for subsequent visits, which further limited the assessment of the impact of study treatment on laboratory parameters.

The strength of the study lies in the fact that it brings out the safety data specific to Saudi Arabia for empagliflozin in patients with T2DM as a regulatory mandate. Furthermore, a PASS for T2DM encompassing and comparing the diabetes-associated complications in the index period and Ramadan period in a single study is practically unavailable. Thus, this study might form a foundation for future follow-up studies on an elaborate scale to yield more profound outcomes.

5. Conclusion

The study evinced empagliflozin in reducing blood glucose levels in patients with T2DM in Saudi Arabia when administered as per the local prescribing information. The outcome was also evaluated during the Ramadan period when all the safety and tolerability parameters were adequately met. Overall, no safety concerns were recognised during the study, thereby underpinning the favourable benefit/risk ratio of empagliflozin. Currently, no update on the empagliflozin prescribing information is deemed necessary. Nonetheless, extensive follow-up studies are warranted to address the study limitations and further complement the study outcomes.

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Disclosure

Dr. Sameh Rakha is the employee of Boehringer Ingelheim.

Data Availability Statement

Data are available on request due to privacy/ethical restrictions. The data that support the findings of this study are available on request from the corresponding author, Dr. Saud Alsifri. The data are not publicly available due to restrictions (containing information that could compromise the privacy of research participants).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Supplementary Table S1. Details of study sites.

S.no.	Type of study site	Investigator name	Site address
1	Active	Dr. Saud Nafa M Alsifri	Al Hada Armed Forces Hospital , AlHada Moutain, Post Box 1347, Taif 21944, SAU
2	Active	Dr. Essa Moharib Aldhafiri	Alalam Medical Center, Khalid Bin Alwaleed St Khalid Ibn Al Walid Street, Al Quds, P.O.Box: 60581, Riyadh 13214, SAU
3	Active	Dr. Mohamed Abdalhameed A. Albhoshi	Alansari Specialist Hospital, Umm Al Qura Road, P.O.Box: 30894, Yanbu 46455, SAU
4	Active	Dr. Thaseena Khaliq	Al Abeer Medical Center, Aziziyah Branch, 7730 Hijazi Al Adawi, Al Aziziyah District -2720 Jeddah 23342 7730, SAU.
5	Active	Dr. Ehab Mahmoud Osman Ali	Saudi German Hospital, Batterjee Road P.O.Box: 2550, Jeddah 21461, SAU
6	Active	Dr. Abdulrahman Mohammed Al Maghamsi	Obesity, Endocrine and Metabolism Center King Fahad Medical City, P.O. Box. 59046, Riyadh 11525, SAU
7	Active	Dr. Hany Abdelbary Elbasyouny	Prince Fahad bin Sultan hospital, Sultanah, P.O.Box:1626, Tabuk 47311, SAU
8	Active	Dr. Saeed Abdelwhab Afify	Shifa Hospital, Al Mansour Street, P.O.Box: 2322, Makkah 24232, SAU
9	Active	Dr. Fathima Bushra Hasan	DAFA Special Polyclinic, Al Samer District, P.O.Box: 12887, Jeddah 21214, SAU
10	Active	Dr. EmadElDin Mohammed Khairy	Al Amal Medical Group, KSA Yanbu Royal Commission Al semeri, P.O.Box: 30530, Yanbu 46455, SAU
11	Active	Dr. Ashraf Shaaban Mahfoez	Ghassan Najeeb Pharaon Hospital, Prince Sultan Street, P.O.Box 4553, Jeddah 21412, SAU
12	Active	Dr. Talaat Sayed Ahmed Allisy	Abha International Private Hospital, Imam Mohammed Bin Saud Road, P.O.Box: 1794, Abha 61431, SAU
13	Active	Dr. Ali Akbar TP	Al Abeer Polyclinic, Bawadi Branch, P.O.Box: 52868, Jeddah 23531, SAU
14	Active	Dr. Salah Fuaad MOHD Al Sayd	Al Rahman Polyclinic, Al Rasaifah, P.O.Box: 9178, Makkah 24232, SAU
15	Active	Dr. Khalid Sayedi	Abha International Private Hospital, Imam Mohammed Bin Saud Road, P.O.Box: 1794, Abha 61431, SAU
16	Active	Dr. Huda Mustafa Khader Dahbour	Al Zafer Hospital, King Abdulaziz Rd, Najran 66261, Saudi Arabia.
17	Active	Dr. Walid Abdelmohsen Shehab Eldin	Saudi German Hospital, 10, King Fahd Road Al-Hijlah District, Aseer 62451, Saudi Arabia
18	Terminated	Dr. Hamzeh Irshaid Alarqan	International Medical Center, Hayel Street, Jeddah 21451, SAU
19	Non recruiting	Dr. Diaa Mansour Ewis	Saudi German Hospital, Batterjee Road P.O.Box: 2550, Jeddah 21461, SAU
20	Non recruiting	Dr. Mohammed Azizullah	Al-Abeer Medical Center, Sharafiyah branch, P.O.Box: 52868, Jeddah 21573, SAU
21	Non recruiting	Dr. Mohamed A. Agag	Riyadh Medical Center, Oruba, Post Box 50768, Riyadh 11533, SAU
22	Non recruiting	Dr. Khaled Abdullah Abdulrahman Tayeb	Al-Noor Specialist Hospital, Kudai, P.O.Box: 6251, Makkah 24241, SAU
23	Non recruiting	Dr. Yasser S. Sheta	Dr.Bakhsh Hospital, P.O.Box: 6940 Jeddah 21452, SAU
24	Non recruiting	Dr. Abdulrahman Abdulmohsen AlShaikh	Dr. Soliman Fakeeh Hospital, Falastin ‹Al-Hamra'a, P.O.Box: 2537, Jeddah 21461, SAU
25	Non recruiting	Dr. Oussama Mohamad Nimr Khatib	Mouwasat Hospital, P.O. Box 3399 Khobar 34234, Alkhobar, Saudi Arabia

Supplementary Table S2. Incidence of DKA and volume depletion in index period by insulin status.

Incidence of DKA in Index Period by Insulin—Yes			
	Empagliflozin (N = 50)	**DPP-4 Inhibitors (N = 26)**	**Rate Ratio**
Patients with events in the period, n(%)	1 (2)	0	
Crude incidence rate	0.020	0	
(95% confidence interval)	(0.005, 0.135)	(0.868, 1)	
Treatment-adjusted incidence rate			
(crude per 1000 patient-years)	1.380	0	0
(95% confidence interval)	(0.035, 7.690)	(0, 5.192)	
Incidence of DKA in Index Period by Insulin Status—No			
	Empagliflozin (N = 701)	**DPP-4 Inhibitors (N = 725)**	**Rate Ratio**
Patients with events in the period, n (%)	0	1 (0.1)	
Crude incidence rate	0	0.001	0
(95% confidence interval)	(0.995, 1.000)	(0, 0.010)	
Treatment-adjusted incidence rate			
(crude per 1000 patient-years)	0	1.407	
(95% confidence interval)	(0, 5.092)	(0.036, 7.842)	
Incidence of Volume Depletion in Index Period by Insulin Status—Yes			
	Empagliflozin N = 50	**DPP-4 Inhibitors N = 26**	**Rate Ratio**
Patients with events in the period, n (%)	1 (2)	0	
Crude incidence rate	0.002	0	0
(95% confidence interval)	(0.005, 0.135)	(0.868, 1.000)	
Treatment-adjusted incidence rate			
(crude per 1000 patient-years)	1.380	0	0
(95% confidence interval)	(0.035, 7.690)	(0, 5.192)	
Incidence of Volume Depletion in Index Period by Insulin Status—No			
	Empagliflozin N = 701	**DPP-4 Inhibitors** N = 725	**Rate Ratio**
Patients with events in the period, n (%)	5 (0.7)	7 (1.0)	
Patients without event, n (%)	696 (99.3)	718 (99.0)	
Crude incidence rate	0.007	0.010	0.700
(95% confidence interval)	(0.002, 0.017)	(0.004, 0.020)	
Treatment-adjusted incidence rate			
(crude per 1000 patient-years)	6.901	9.852	0.700
(95% confidence interval)	(2.241, 16.105)	(3.961, 20.299)	
Time from start of period to first occurrence in period (days)	180 ± 143.4	256.1 ± 110.5	

Abbreviation: DKA: Diabetic ketoacidosis; DPP-4: Dipeptidyl peptidase-4.