Non-interventional Study Protocol

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Document Number:	**<document number>**
BI Study Number:	1245.149
BI Investigational Product(s):	Jardiance® (EMPAGLIFLOZIN)
Title:	Post-authorization safety study in patients with type 2 diabetes mellitus to assess the incidence of ketoacidosis, severe complications of urinary tract infection, volume depletion, and dehydration among patients treated with EMPAGLIFLOZIN or DPP-4 inhibitors in Saudi Arabia
Brief lay title	Post-authorization safety study in type 2 diabetic patients in Saudi Arabia treated with EMPAGLIFLOZIN to assess the incidence of ketoacidosis, severe complications of urinary tract infection, volume depletion, and dehydration
Protocol version identifier:	2
Date of last version of protocol:	*2017-07-25*
PASS:	*"Yes"*
EU PAS register number:	*If applicable, insert registration number in the EU PAS register; indicate "Study not registered" if the study has not been registered in the EU PAS register*
Active substance:	Jardiance® (EMPAGLIFLOZIN 5mg & 10 mg)
Medicinal product:	Jardiance® film-coated tablets 10mg, 25mg
Product reference:	*Reference number(s) of centrally authorised products and/or, if possible, of nationally authorised products subject to the study*
Procedure number:	*SFDA application no. 17062102 on SCTR*
Marketing authorisation holder(s):	Boehringer Ingelheim Saudi Arabia
Joint PASS:	No
Research question and objectives:	NIS with new data collection, with the following aims: Primary outcomes

	To estimate the incidence of: - Ketoacidosis - Severe urinary tract infections - Volume depletion - Dehydration in type 2 diabetes mellitus (T2DM) patients exposed to EMPAGLIFLOZIN compared with the incidence in T2DM patients exposed to Dipeptidyl peptidase-4 (DPP-4) inhibitors Secondary outcomes To estimate the risk of each primary outcome with respect to the following definition of exposure: the Ramadan period
Country(-ies) of study:	Multi-Centre study conducted in Saudi Arabia
Author:	Dr. Thamer AlShammary
Marketing authorisation holder(s):	*Boehringer Ingelheim*
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Date:	23 January 2017
Page 1 of 44	

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ACR	Albumin Creatinine Ratio
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
BI	Boehringer Ingelheim
BP	Blood Pressure
CA	Competent Authority
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRO	Contract Research Organization
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DMP	Data Management Plan
DPP-4	Dipeptidyl-peptidase 4

E-CRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EU	European Union
EU PAS	European Union electronic register of post-authorization studies
EU-QPPV	European Union-Qualified Person for Pharmacovigilance
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GLUT	Glucose Transporter
GPP	Good Pharmacy Practice
HbA1c	Glucosylated Hemoglobin
HDL-C	High Density Lipoprotein Cholesterol
IC50	Inhibitory Concentration
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
LDL-C	Low Density Lipoprotein Cholesterol
LPVM	Local PV Manager
MAH	Marketing Authorisation Holder Activities
MedDRA	Medical Dictionary for Drug Regulatory Activities
MFDS	The Ministry of Food and Drug Safety

3. RESPONSIBLE PARTIES

Boehringer Ingelheim (BI) has appointed a Trial Clinical Monitor (TCM), responsible for coordinating all required activities, in order to

- manage the study in accordance with applicable regulations and internal standard operating procedures (SOPs).
- direct the study team in the preparation, conduct, and reporting of the trial,
- order the materials as needed for the study,
- ensure appropriate training and information of Local Clinical Monitors (CMLs), Clinical Research Associate (CRAs), and Investigators of Saudi Arabia.

The organization of the study will be done by a Contract Research Organization (ClinTec) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the study. A CML will be appointed responsible for coordinating the activities required in order to manage the study in accordance with applicable regulations and internal SOPs in the countries covered by the respective BI OPU. On-site monitoring will be performed by a CRO appointed by BI.

An Investigator Site File (ISF) containing all relevant study related documentation will be maintained according to local regulations and BI SOPs at each study site. A copy of the ISF documents will also be kept as an electronic Trial Master File (TMF) at BI according to BI SOPs. Documents related to participating physician and other important participants, especially their curricula vitae, will be filed in the TMF.

4. ABSTRACT

Name of company: Boehringer Ingelheim Saudi Arabia			
Name of finished medicinal product: EMPAGLIFLOZIN®			
Name of active ingredient: EMPAGLIFLOZIN			
Protocol date: 20 Nov 2016	**Study number:** 1245.149	**Version/Revision:** **1.0**	**Version/Revision date:**
Title of study:	Post-authorization safety study in patients with type 2 diabetes mellitus to assess the incidence of ketoacidosis, severe complications of urinary tract infection, volume depletion, and dehydration among patients treated with EMPAGLIFLOZIN or DPP-4 inhibitors in Saudi Arabia		
Rationale and background:	According to the local regulations, for some safety concerns, additional pharmacovigilance activities, for instance post-authorization safety studies which are initiated, managed or financed by marketing authorization holders, voluntarily, or pursuant to obligations can be imposed by SFDA. SFDA has requested a non-interventional study (NIS) to provide supplementary data to monitor the safety of EMPAGLIFLOZIN in a real-life situation including the Ramadan period.		
Research question and objectives:	Non-interventional study with new data collection, with the following aims: <u>Primary outcomes</u> To estimate the incidence of: - Ketoacidosis - Severe urinary tract infections - Volume depletion - Dehydration in type 2 diabetes mellitus (T2DM) patients initiating EMPAGLIFLOZIN compared with the incidence in T2DM patients initiating Dipeptidyl peptidase-4 (DPP-4) inhibitors <u>Secondary outcomes</u> To estimate the risk of each primary outcome with respect to the following definition of exposure: the Ramadan period		
Study design:	This will be non-interventional study with new data collection. The		

	study will use a “new users” design and compare new users of EMPAGLIFLOZIN to new users of DPP-4 inhibitors. The index date will be defined as the date on which each identified new user receives the index prescription for EMPAGLIFLOZIN or a DPP-4 inhibitor. Number of recruited patients will be comparable in each group within a given timeframe (i.e. each site will ensure to recruit similar number per month for each group). Propensity scores based on information prior to the index date will be used to account for potential confounding. Patients will be follow-up for 12 months after index date.

Population:	Patients diagnosed with T2DM in Saudi Arabia The study population will include patients aged at least 18 years and diagnosed with T2DM in Saudi Arabia and who will initiate EMPAGLIFLOZIN treatment during the study period and who have not used other SGLT2 inhibitors during the previous 12 months. Patients switching to or adding EMPAGLIFLOZIN to other antidiabetic medications will be compared to patients switching to or adding comparator treatment on same background therapy. This modification of a "new-user" design is an appropriate method for studying second-line therapies in chronic conditions [R13-1120]. The comparator groups will include new users of DPP-4 inhibitors. The same inclusion and exclusion criteria will be applied. Patients with a confirmed diagnosis of type 1 diabetes before or after the index date will not be included in the study. Patients prescribed fixed-dose combinations of SGLT2 inhibitors with DPP-4 inhibitors will be excluded.
Variables:	*Covariates:* Variables potentially associated with outcomes of interest—such as sociodemographic variables including age, sex, ; concomitant medications; will be identified for all cohort members prior to and including the index date. Severity of T2D will be assessed by HbA1c values concomitant diagnoses and duration since the first diagnosis, when available. These and other variables that can differ by exposure group will be considered for inclusion as predictors in the logistic regression models used to generate the propensity scores. Propensity scores will be used in the analysis to quantify the probability of receiving EMPAGLIFLOZIN at the index date for new users of both EMPAGLIFLOZIN and DPP-4 inhibitors. At the index date, cohort members will also be classified by indicator variables on the calendar time of cohort entry (by quarter) whether the index treatment (EMPAGLIFLOZIN or DPP-4 inhibitor) was added to existing medication (adding on), or if the index treatment was initiated as a replacement for another GLD (switching from the existing GLD to EMPAGLIFLOZIN or DPP-4 inhibitor), and whether this treatment was received as monotherapy or as dual or triple therapy. A variable indicating whether or not patients were receiving insulin at the index date will also be created.
Data sources:	The investigator will be asked to successively write in the case report forms (e-CRFs) from the subject who was initially administered the

	drug following the study start date to the requested number of subjects without omission. Data on the period preceding the index date will be collected at the time of the first survey. Prior to initiation of the study, written contract shall be concluded, and this contract shall be concluded with the head of the site or the investigator with his/her consent. Field study with new data collection

Study size:	Based on the requirements of SFDA, the sample size will be 1500 patients overall, 750 patients in each group DPP4i and Empagliflozin.The recruitment process will be adjusted in each site accordingly.
Data analysis:	For the incident users of EMPAGLIFLOZIN and of DPP4i, analysis will be performed using the "as-treated" (AT) approach. This corresponds to censoring individuals who discontinue use of the index drug, i.e. either switch from the index drug to any other of the index drug (EMPAGLIFLOZIN or DPP-4 inhibitor) during follow-up or stop using the index drug. For the assessment of the primary and secondary objectives, the main data analysis will be conducted in two stages: - Construction of the propensity score (PS) by modelling the exposure to EMPAGLIFLOZIN vs. DPP-4 inhibitor - Estimation of the effect of exposure to EMPAGLIFLOZIN on the ketoacidosis, severe urinary tract infections, volume depletion and dehydration compared to those exposed to DPP-4 inhibitor. Additional sensitivity analyses will be performed to validate the robustness of alternative definitions of outcome, exposure, covariates and reduction of bias due to matching. The following estimates and comparison will be generated: - Crude and adjusted incidence rates of each of the outcomes among EMPAGLIFLOZIN new users and among DPP-4 inhibitor new users. Incidence rates will be reported as point estimates (in cases per 1,000 person-years) and 95% confidence intervals (CIs). - Summary IRRs, after adjusting (via stratified Mantel-Haenszel analysis) for propensity score deciles and calendar year, among EMPAGLIFLOZIN new users versus DPP-4 inhibitor new users. - Adjusted IRRs for each of the outcomes will be the main effect estimates of interest. Adjusted incidence rates and IRRs will be calculated by weighting the incidence or IRR of each stratum (defined by propensity score decile and calendar year) by the amount of EMPAGLIFLOZIN person-time within the stratum. - An additional analysis will further stratify the IRRs by categories of insulin use at the index date. - Additional sensitivity analyses will be performed to evaluate potential for bias and confounding.
Milestones:	Data collection will start in Oct 2017; The Final report will be produced using data through 12 months from the start of use of Empagliflozin or DPP4I index date (currently planned study period data collection from Oct 2017 – Jun 2019).

5. AMENDMENTS AND UPDATES

NONE

6. MILESTONES

Milestone	**Planned Date**
IRB/IEC approval	Oct 2017 – Mid Dec 2017
Start of data collection (trial data) FPI	Oct 2017
Ramadan Month 2018	May 14th, 2018 – June 13th, 2018 ±1-2 days
Ramadan Month 2019	May 5th, 2019 – Jun 4th, 2019 ±1-2 days
End of data collection (LPV)	End of Jun 2019
Final report of study results: CSR preparation	Dec 2019

7. RATIONALE AND BACKGROUND

Around 415 million patients are affected by DM worldwide. DM is considered an epidemic in many countries of the world, and the number of people affected is expected to double over the next decade. DM is a major leading cause of many complications and diseases such as heart diseases and several types of infections. T2DM is more common than type 1, comprising 90-95% of all DM cases. Over 5 million people died from DM in 2015 worldwide. In the Middle East and North Africa, around 36 million patients were affected by DM in 2015, a number expected to rise to 72 million patients by 2040. Saudi Arabia has one of the highest prevalence of DM in the world with over 20% of the population affected. Empagliflozin is a selective sodium/glucose co-transporter 2 (SGLT2) inhibitors one of the most recent classes of drugs used to treat T2DM. SGLT2 inhibitors promote the renal excretion of glucose and help lower elevated blood glucose levels in patients with T2DM. In Saudi Arabia, It is indicated for treatment of T2DM as monotherapy or add-on combination therapy. It is used as monotherapy when exercise and diet control alone do not provide glycaemic control in patients for whom use of metformin is considered inappropriate because of intolerance. It is also used in combination with other glucose lowering agents—including insulin—when they do not provide adequate glycaemic control. Several clinical trials showed the efficacy of empagliflozin in reducing the blood glucose level. Furthermore, empagliflozin is a unique drug among all hypoglycaemic agents because it has shown a reduction in major cardiovascular events, which has not been the case with other oral hypoglycaemic agents. Empagliflozin, as other SGLT2 inhibitors, is associated with some adverse reactions such as urinary tract infections and genital infections, especially in females. In addition, rare cases of diabetic ketoacidosis (DKA) have been reported. In parallel to the launch of SGLT2 inhibitors in Saudi Arabia, the Saudi Food and Drug Authority (SFDA) has requested a non-interventional study to further monitor the safety of empagliflozin in the country, including during the Ramadan period.

The objectives of this study are to assess the risk of ketoacidosis, severe urinary tract infections, volume depletion, and dehydration associated in patients with T2DM initiating empagliflozin compared to patient initiating a dipeptidyl peptidase-4 (DPP-4) inhibitors over a 12-month period of follow-up, including the month of Ramadan.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 PRIMARY OBJECTIVE

Non-interventional study with new data collection, with the following aims:

Primary outcomes

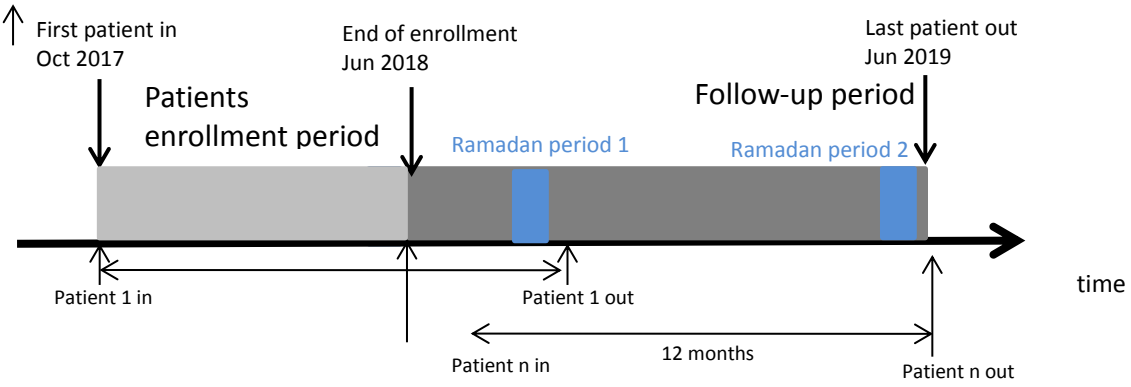
To estimate the incidence of:

- Ketoacidosis
- Severe urinary tract infections
- Volume depletion
- Dehydration

in T2DM patients initiating EMPAGLIFLOZIN compared with the incidence in T2DM patients initiating Dipeptidyl peptidase-4 (DPP-4) inhibitors.

8.2 SECONDARY OBJECTIVE

To estimate the risk of each primary outcome with respect to the following definition of exposure:
- The Ramadan period
(1st day of Ramadan to 29th day of Ramadan based on the Islamic Hijri calendar)



9. RESEARCH METHODS

This is a non-interventional study with new data collection.
This study will cover the period between 20 Mar 2017 (start of feasibility) and 31 Dec 2019. The main goals of this study are to examine the risk of ketoacidosis, severe urinary tract infections, volume depletion, and dehydration associated with the use of EMPAGLIFLOZIN compared to the use of DPP-4 inhibitors in T2DM patients. The study will use an "incident users" design and compare new users of EMPAGLIFLOZIN with new users of DPP-4 inhibitors. The index date will be defined as the date on which each identified new user receives the index prescription for EMPAGLIFLOZIN or DPP-4 inhibitors. The definition of drug exposure for EMPAGLIFLOZIN will be any patient using at least one prescription of EMPAGLIFLOZIN tablets (10 or 25 mg) or fixed-dose combinations with metformin. The comparator group will be comprised of patients with at least one prescription of a DDP-4 inhibitor: sitagliptin, saxagliptin, linagliptin, vildagliptin, alogliptin (and fixed-dose combinations of these drugs with metformin). Each member of the population exposed to EMPAGLIFLOZIN must have at least one prescription for EMPAGLIFLOZIN, with or without other Glucose-lowering Drugs (GLDs,) and no prior prescriptions of a DPP-4 inhibitor or EMPAGLIFLOZIN during the available pre-index period. Each member of the population exposed to a DPP-4 inhibitor must have at least one prescription for a DPP-4 inhibitor, with or without other GLDs, and no prior prescriptions of a DPP-4 inhibitor or EMPAGLIFLOZIN during the available pre-index period.

Follow-up will start the day after the index date and will continue until any of the following conditions are met: date of death or after 12 months of follow-up, or the date during follow-up that specific exclusion criteria are met, the date of the last continuous treatment of the index drug (EMPAGLIFLOZIN or DPP-4 inhibitor) plus a defined grace period (30 days after the end of the last prescription's days' supply in main analyses), or the date in which a new treatment episode starts with any of the other index drugs. Patients who discontinue an index drug and then subsequently initiate another index drug will not be allowed to re-enter the study. Patients will be followed-up for 12 months.

This study will be carried out in the manner of successive surveys that the investigator will be asked to successively write in the case report forms (e-CRFs) from each subject who was initially administered the drug following the study start date until the requested number of subjects is reached. Number of recruited patients will be comparable in each group within a given timeframe (i.e. each site will ensure to recruit similar number per month for each group).

Prior to initiation of the study, a written contract shall be concluded, and this contract shall be executed among BI OPU, CRO with the head of the site or the investigator with his/her consent.
Patients will be managed according to the local practice guidelines. The choice of treatment will be solely at the discretion of the participating physician. EMPAGLIFLOZIN and the

comparator DPP-4 inhibitor will be administered according to the approved labels in Saudi Arabia. Hence there are no additional risks to patients by participating in this PASS.

9.1 STUDY DESIGN

This is a non-interventional study with new data collection from T2DM patients in Saudi Arabia. The study will use a "new users" design and compare new users of EMPAGLIFLOZIN to new users of DPP-4 inhibitors in T2DM patients. We have chosen DDP-4 inhibitors because they are considered one of the new groups of hypoglycaemic agents, and they are one of the options to treat patients with T2DM as they have similar indications to EMPAGLIFLOZIN.

Number of recruited patients will be comparable in each group within a given timeframe (i.e. each site will ensure to recruit similar number per month for each group).

The index date will be defined as the date on which each identified new user receives the index prescription for EMPAGLIFLOZIN or DPP-4 inhibitors. The patients will be followed up for 12 months after the index date.

The incident-user design avoids comparing a population predominantly composed of first-time users of a newly marketed drug such as EMPAGLIFLOZIN with a population of prevalent users of an older drug who may have stayed on the comparator treatment for a longer time and be less susceptible to the events of interest.

EMPAGLIFLOZIN® and the comparator DPP-4 inhibitor will be prescribed according to the local label and at the discretion of the treating physician. Since this is a non-interventional study, the drug will not be supplied by the sponsor. Furthermore, the sponsor will not cover the expenses related to other medications taken by the patient, interventions, procedures, or diagnostic test.

9.2 SETTING

9.2.1 Study sites

A total of 1500 patients will be enrolled at approximately 25 sites in Saudi Arabia. The treating physicians will mainly be general practitioners (GPs) and/or specialists including endocrinologist, diabetologist & internists. Number of recruited patients will be comparable in each group within a given timeframe (i.e. each site will ensure to recruit similar number per month for each group).

9.2.2 Study population

Main diagnosis for study entry

Patients diagnosed with T2DM will be included.

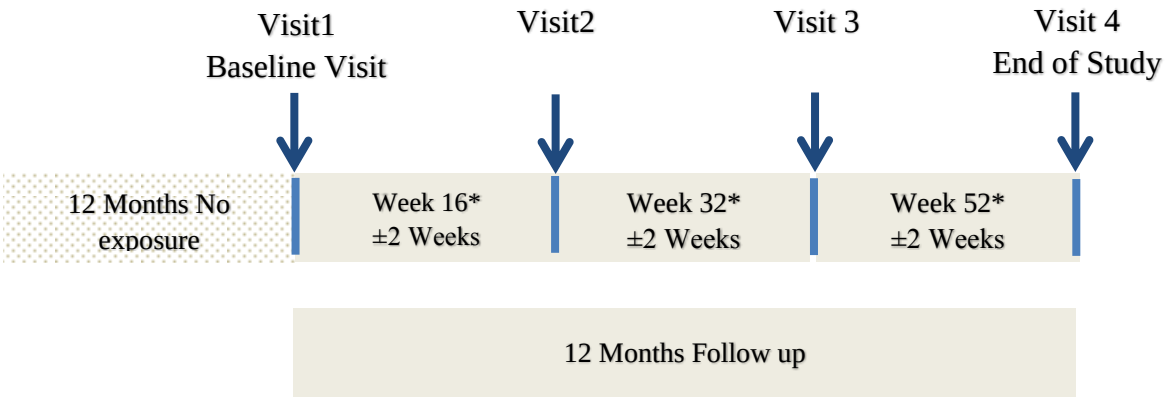
Inclusion criteria:

- Patients who have signed Informed consent form.
- The patients will be at least 18 years old at index date, diagnosed with T2DM in Saudi Arabia, and who will initiate EMPAGLIFLOZIN treatment during the study period who have not used other SGLT2 inhibitors during the previous 12 months.
- The diagnosis of T2DM will be based on American Diabetes Association (ADA) criteria: a fasting plasma glucose (FPG) level of 126 mg/dL (7.0 mmol/L) or higher; a 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test (OGTT); a random plasma glucose of 200 mg/dL (11.1 mmol/L) or higher in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis.[15] Moreover, an HbA1c of 48 mmol/mol (6.5%) can be used as the cut off point for diabetes diagnosing or, however, the previous test is not done by all health institutions. The diagnosis should be based on confirmation tests (i.e. signs and symptoms and not only on one single test. Furthermore, if the health institution is using the International Statistical Classification of Diseases and Related Health Problems (ICD) in version 9 or 10, these codes will be used to determine the patients with T2DM. These codes will be confirmed by the abovementioned criteria. The codes for T2DM in ICD-9 will be 250.00 or 250.02 or in ICD-10-CM will be E11.xx.[16, 17]

Exclusion criteria:

- Known hypersensitivity to EMPAGLIFLOZIN, the comparator DPP-4 inhibitors or any of their excipients
- Patients for whom EMPAGLIFLOZIN or the comparator DPP-4 inhibitor is contraindicated according SFDA approved label
- Patients prescribed fixed-dose combinations of SGLT2 inhibitors with DPP-4 inhibitors will be excluded.
- The same inclusion and exclusion criteria will be applied to the comparator group, which will include new users of DPP-4 inhibitors.

- **Study visits**



* From Visit 1

Baseline Visit

9.2.2.1 Visit 1; Baseline Visit

Upon patient enrolment, the following available data will be recorded on the patient's e-CRF.

- Visit date
- Diagnosis: date of the diagnosis of T2DM, Family history of T2DM
- Inclusion / Exclusion criteria
- Informed consent form: Date of Informed consent
- Demographic data: Age, gender,
- Diabetes mellitus related complication (Retinopathy, Neuropathy, Nephropathy)
- Medical history: Hypertension, Dyslipidaemia, Coronary artery disease, Stroke, Liver disease, Renal failure, Renal Transplant, Renal Stones Nephropathy, Prostate Diseases, Pancreatitis, Surgery, Infections (other than UTIs) and heart diseases, other (history of concomitant disease within 6 months). In addition, genital defects, urinary tract anatomical defects, when available.
- Baseline lab variables when available – Complete Blood Count (CBC), Oral Glucose Tolerance Test (OGTT), ketones level, amylase, lipase, arterial blood gas, pH, bicarbonate, lipid profile tests, Blood Urea Nitrogen (BUN), liver tests, International Normalized Ratio (INR) for prothrombin time and platelets
- Physical examination: body mass index (BMI), blood pressure, pulse rate, weight
- Baseline HbA1C, blood glucose level (if available)
- Renal Function: record Serum creatinine, eGFR, urine ACR if results are available (collected within the latest 2month period)(if available)

- Concomitant anti-hyperglycemic agent: record any anti-hyperglycemic agents have been taken prior to the baseline visit (within 6 months prior to baseline)
- Concomitant medications: record all medications have been taken at least once since one month prior to the baseline visit.
- Dose of EMPAGLIFLOZIN / DPP4-Inhibitor given
- PASS physician's electronic signature for data integrity

At visit 1, the patient will be requested to contact the treating physician in the event of any adverse events noted after initiating EMPAGLIFLOZIN® or the comparator DPP-4 inhibitor treatment.

9.2.2.2 Visit 2; 16±2 weeks from Visit 1

After 16±2 weeks from Visit 1, the patients will return for follow-up. The followings will be noted and recorded in the e-CRF.

- Visit date
- Physical examination: blood pressure, pulse rate, weight (if available)
- HbA1C (if available)
- Any change of EMPAGLIFLOZIN® or comparator DPP-4 inhibitor given
- Concomitant anti-hyperglycemic agent including new medications taken since last visit: any change in the concomitant medications (dose and dosing intervals)
- Concomitant medications including new medications taken since last visit: any change in the concomitant medications (dose and dosing intervals)
- Any adverse events noted
- Study completion status
- Discontinuation or continuation (if interruption, date of last administration, reason for interruption
- PASS physician's electronic signature for data integrity

9.2.2.3 Visit 3; 32±2 weeks from Visit 1

After 32±2 weeks from Visit 1, the patients will return for follow-up. The followings will be noted and recorded in the e-CRF.

- Visit date
- Physical examination: blood pressure, pulse rate, weight (if available)
- HbA1C (if available)
- Any change of EMPAGLIFLOZIN® or comparator DPP-4 inhibitor given

- Concomitant anti-hyperglycaemic agent including new medications taken since last visit: any change in the concomitant medications (dose and dosing intervals)
- Concomitant medications including new medications taken since last visit: any change in the concomitant medications (dose and dosing intervals)
- Any adverse events noted
- Study completion status
- Discontinuation or continuation (if interruption, date of last administration, reason for interruption
- PASS physician's electronic signature for data integrity

9.2.2.4 Visit 4; 52 weeks End of study

- Visit date
- Physical examination: blood pressure, pulse rate, weight
- HbA1C (if available)
- Any change of EMPAGLIFLOZIN® or comparator DPP-4 inhibitor given
- Concomitant anti-hyperglycaemic agent including new medications taken since last visit : any change in the concomitant medications (dose and dosing intervals)
- Concomitant medications including new medications taken since last visit : any change in the concomitant medications (dose and dosing intervals)
- Any adverse events noted
- Discontinuation or continuation (if interruption, date of last administration, reason for interruption
- PASS physician's electronic signature for data integrity

9.2.2.5 Follow-up period

Follow-up will start the day after the index date and last until end of study data (date of death or date of study end), the date during follow-up when specific exclusion criteria are met, the end date of the treatment of the index drug (EMPAGLIFLOZIN or other SGLT2 inhibitor or DPP-4 inhibitor) plus a defined grace period (30 days after the end of the last prescription's supply in main analyses), or the date on which a new treatment episode starts with any of the other index drugs.
Patients with adverse events noted at the final follow-up visit or upon premature discontinuation of EMPAGLIFLOZIN or the comparator DPP-4 inhibitor will be monitored further until the resolution of those adverse events. Alternatively, those patients will be followed up until the PASS physician and sponsor agree that no further follow-up is necessary.

9.2.3 Study discontinuation

Boehringer Ingelheim reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Emergence of any efficacy/safety information that could significantly affect continuation of the study, or any other administrative reasons.
3. Violation of Good Clinical Practice (GCP) (as applicable), the study protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study

The investigator / the study site will be reimbursed for reasonable expenses incurred in case of study termination (except in case of the third reason).

9.3 VARIABLES

9.3.1 SAFETY

9.3.1.1 Outcomes of safety

All reported adverse events in patients who take at least one dose of EMPAGLIFLOZIN or comparator DPP-4 inhibitor will be reported.
All documented information in the e-CRF will be analyzed at the end of the study. At the time of analysis, safety outcomes will be analyzed based on the current versions of MedDRA & BIcMQs

9.3.2 Exposures

The definition of drug exposure for empagliflozin will be any patient using at least one prescription of empagliflozin tablets (10 or 25 mg) or fixed-dose combinations with metformin. For the comparator group, the patients will have at least one prescription of DDP-4 inhibitors. DDP-4 inhibitor users included in this study will be using one of the following approved drugs in Saudi Arabia: sitagliptin, saxagliptin, vildagliptin, alogliptin, linagliptin, or fixed-dose combinations of these drugs with metformin.[18]
Furthermore, each member of the population exposed to empagliflozin must have at least one prescription for empagliflozin, with or without other glucose-lowering drugs (GLDs), and have no prior prescriptions of a DPP-4 inhibitor or empagliflozin during the available pre-index period. Each member of the population exposed to a DPP-4 inhibitor must have at least one prescription for a DPP-4 inhibitor, with or without other GLDs, and no prior prescriptions of a DPP-4 inhibitor or empagliflozin during the available pre-index period. Add-on therapy will be allowed after using the exposure of interest as the initial drug for new users. Therefore, using the drug as part of dual therapy or triple therapy will be allowed.
The use of studied medications will be defined on different levels: current use, recent use and discontinuation of the studied drugs. Current use of the index drugs will be defined from the date of prescription of empagliflozin or DPP-4 inhibitor to the end of supply for that prescription plus a period of 30 days. Recent use will be defined from the end of current use (30 days after end of supply) until 90 days later (which is 120 days after end of supply). Discontinuation of the index drug will be defined as no further prescription 120 or more days

after the end of the last prescription's supply. Patients who discontinue an index drug and then subsequently initiate another index drug will not be allowed to re-enter the study. Patients switching to or adding Empagliflozin to other antidiabetic medications will be compared to patients switching to or adding comparator treatment on the same background therapy. Identification of a "new-user" design is an appropriate method for studying second-line therapies in chronic conditions.
During the statistical analyses, analyses will be stratified by treatment complexity (mono vs. dual vs. triple therapy) and by calendar time of treatment initiation. Prior or current use of insulin is allowed; an additional stratified analysis by insulin use is planned. Propensity scores based on information prior to the index date will be used to account for potential confounding.

9.3.3 Outcomes

This study proposed to assess and evaluate the risk of ketoacidosis, severe urinary tract infections, volume depletion and dehydration associated with the use of empagliflozin compared with the use of DPP-4 inhibitors in T2DM. As per ADA, ketoacidosis is defined as a serious condition because of inability of body cells to get glucose as a source of energy, and subsequently, the body produces ketones as the result of burning fat for energy. DKA occurs because of a lack of insulin in the body, not enough food intakes in diabetic patients and insulin reaction (low blood glucose). It is characterized by high ketones levels, positive ketones in the urine and high pH levels. Specifically, for the SGLT2i induced DKA the blood glucose level may not be increased above 240 mg/dl. [19] ¬The second outcome, which is severe urinary tract infection, is defined as pyelonephritis or urosepsis. Volume depletion is the reduction in the extracellular fluids. This differs from dehydration, which is the loss of total body water that leads to hypertonicity. To ascertain the outcome diagnosis, signs and symptoms along with the laboratory tests results will be used.

All identified primary outcomes will be evaluated also during the period of the month of Ramadan.

9.3.4 Covariates

The covariates of interest are age, gender, body mass index (BMI), blood pressure, blood glucose level, and HbA1c, if available. Comorbidities of interest include hypertension, dyslipidaemia, kidney diseases, kidney stones, history of kidney transplant, liver diseases, prostate diseases, pancreatitis, surgery, infections (other than UTIs) and heart diseases, if available. In addition, genital defects, urinary tract anatomical defects, lab variables (CBC, FPG, OGTT, ketones level, amylase, lipase, arterial blood gas, pH, bicarbonate, ScCr, lipid profile tests, BUN, liver tests, INR and platelets) and concomitant medications (especially those are risk factors to the outcomes of interest) will be considered as covariates. All these covariates will be identified, if available, for all cohort members prior to and including the index date. Severity of T2DM will be assessed by HbA1c values, concomitant diagnoses and duration since the first diagnosis, when available.
These and other variables that can differ by exposure group will be considered for inclusion as predictors in the logistic regression models used to generate the propensity scores.

Propensity scores will be used in the analysis to quantify the probability of receiving empagliflozin at the index date for new users of both empagliflozin and DPP-4 inhibitors. At the index date, cohort members will also be classified by indicator variables on the calendar time of cohort entry (by quarter) whether the index treatment (empagliflozin or DPP-4 inhibitor) was added to existing medication (adding on), or if the index treatment was initiated as a replacement for another GLD (switching from the existing GLD to empagliflozin or DPP-4 inhibitor), and whether this treatment was received as monotherapy or as dual or triple therapy. A variable indicating whether or not patients were receiving insulin at the index date will also be created.

List of Variables, (other variables will be added during the study period)
Demographics
1. Age
2. Gender

Hospitalization, when available
3. Admission date
4. Place admitted from
5. Outcomes diagnosis date
6. Place of diagnosis (ER, Inpatients, Outpatient)

Treatment
7. Treatment initiation date
8. Treatment discontinuation date

Outcomes, when available
9. Date of DKA diagnosis
10. Date of UTI diagnosis
11. Date of dehydration diagnosis
12. Date of volume depletion diagnosis
13. Date of death
14. Primary cause of death
15. Date of discharge
16. Date of admission
17. Reason for admission

Lab variables / Vital signs, when available

18. Weight
19. Height
20. CBC
21. Blood glucose
22. HbA1c
23. FPG
24. OGTT
25. Ketones

26. Blood pressure
27. Amylase
28. Lipase
29. Triglyceride (TG)
30. Liver tests
31. Arterial blood gas
32. pH
33. Bicarbonate
34. Lipid profile tests
35. INR
36. eGFR
37. CrCl
38. ScCr
39. BUN
40. Platelets

Comorbidities, Medical History

41. Diabetes
42. Kidney diseases
43. Hypertension
44. Heart failure
45. Acute coronary diseases
46. Heart diseases
47. Pregnancy
48. Abdominal trauma
49. Kidney stones
50. Body paralysis (paraplegia or quadriplegia)
51. Pancreatitis
52. Dyslipidaemia
53. Cerebrovascular disease
54. Pulmonary disease
55. Hypothyroidism
56. Hyperthyroidism
57. Surgery
58. Liver disease
59. HIV/AIDS
60. Cancer
61. Hepatitis “A,B,C”
62. Cholestatic hepatitis
63. Acute liver disease
64. Liver cirrhosis
65. Kidney transplant

66. Prostate diseases
67. Burns
68. Genital defects
69. Urinary tract anatomical defects
70. Other liver diseases

Prior medications exposure in the last 6 months and during the study period

71. Empagliflozin
72. Sitagliptin
73. Saxagliptin
74. Vildagliptin
75. Alogliptin
76. Linagliptin
77. Insulin (all types)
78. Metformin (single or combination)
79. Sulfonylureas
80. Meglitinides
81. Thiazolidinediones
82. α-glucosidase inhibitors
83. Glucagon-like peptide-1 receptor
84. Antihyperlipidemics (Statins, Fibrates, Niacin)
85. Antihypertensive agents (Diuretics, ACEIs, B-blocker)
86. Antipsychotic medications
87. Corticosteroids
88. Tacrolimus
89. Glucagon
90. Interferon
91. Albuterol
92. Dopamine
93. Dobutamine
94. Terbutaline
95. Ritodrine

9.4 DATA SOURCES

This study will be carried out in the manner of successive survey that the investigator will be asked to successively write in the case report forms (e-CRFs) from the subject who was initially administered the drug following the study start date to the requested number of subjects without omission. Prior to initiation of the study, a written contract shall be concluded, with the head of the site or the investigator with his/her consent for field study with new data collection.

This study will be carried out in the manner of successive surveys where the investigator will be asked to write in the case report forms (e -CRFs). Number of recruited patients will be comparable in each group within a given timeframe (i.e. each site will ensure to recruit similar number per month for each group). Data on the period preceding the index date will be collected at the time of the first survey.

The site(s) will be primary care clinics, hospital clinics and other outpatient clinics. Data from hospitals will be documented when needed, especially if there are cases of admission for one of the study outcomes. Discharge data will always be documented by the investigator when needed.
Demographics (age, gender), comorbidities (cardiac, hepatic, oncologic, renal, neurologic, immunologic, respiratory and vascular), previous and current hypoglycaemic agent exposures (biguanides, sulfonylureas, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, α-glucosidase inhibitors, glucagon-like peptide-1 receptor agonists and insulin), and laboratory data (complete blood count, blood glucose level "all available types", and HbA1c) variables will be obtained from either the medical record or during the first survey (appendix A).

9.5 STUDY SIZE

The sample size is of 1500 patients; it is based on SFDA requirements. As per SFDA regulation and requirements to detect the DKA cases, 750 patients will be enrolled in each group (DPP4i and SGLT-2i). The number of recruited patients will be comparable in each group within a given time frame (i.e. each site will ensure to recruit similar number per month for each group as much as possible). In addition, prevalence of the primary outcomes was searched in literature and a study found assuming the prevalence to be around 25% (urinary tract infection and other risk factors) among Saudi patients with diabetes.

9.6 DATA MANAGEMENT

Patients' data will be gathered by e-CRF. The data management procedures to ensure the quality of the data are described in detail in the data management plan (DMP) available in TMF. Data management and statistics will be outsourced to a qualified contract research organization (CRO).

9.7 DATA ANALYSIS

Details of all analyses and variables specification will be defined in a separate SEAP.

Patients are grouped according the exposure to either EMPAGLIFLOZIN or DPP-4 inhibitors. Data will be analysed per group. Let the index period define the time from index date to the end of treatment as defined in section 9.3.2 by current use, and the follow-up period the time from index date to the end of observation as defined in section 9. Incidences will be derived if events of interest occur in the respective period. The main analysis will

consider index periods only, a secondary analysis will consider only the time of the index period in the month of Ramadan in every year, while sensitivity analyses will consider respective follow-up periods, overall or during Ramadan only. Times from index date to first occurrence will also be determined per event of interest and described by means of Kaplan-Meier estimates and median times with 95% confidence intervals, where appropriate.

All individual data will be listed and described per group by means of summary tables presenting frequency counts and percentages for categorical data and arithmetic means, standard deviations, medians, minimum and maximum values for continuous data. Baseline is defined as the last observation on or before the index date.

For the assessment of the primary and secondary objectives, the main data analysis will be conducted in two stages:

1) Construction of the PS by modelling the exposure to EMPAGLIFLOZIN vs. DPP-4 inhibitor;
2) Estimation of the effect of exposure to EMPAGLIFLOZIN on the risk of ketoacidosis, severe urinary tract infections, volume depletion and dehydration compared to those exposed to DPP-4 inhibitor.

Propensity score stratification will be the primary method to control for the confounders in the analysis phase. The stratification will divide the study population in several groups (max. 5 groups) based on their propensity score value. Propensity score matching will also be used as secondary method in the analysis phase.

All statistical tests will be conducted with a two-sided significance level alpha of 0.05 and all analyses will be conducted using SAS statistical analysis software version 9.4 (SAS Institute, Inc., Cary, NC) or later.

9.7.1 Propensity score modelling

A propensity score (PS) method will be utilized to control for confounding in the analysis phase. It is used to balance the baseline covariates predictive of treatment, to lessen the unequal chance of receiving EMPAGLIFLOZIN versus DDP-4 inhibitors. PS will be estimated with logistic regression for each cohort member. PS is one of effective methods used in epidemiological studies analyses.
Bivariate analysis will be initially used for the selection of potential clinical covariates for inclusion in the propensity score model. Demographic and clinical categorical data will be analysed using an χ^2 or Fisher's exact test while continuous variables will be analysed using a student's t-test or Mann-Whitney U test.
The model will be selected in a process optimizing the goodness of fit. Only clinically relevant, statistically significant (p-value <0.25) covariates will be included. Propensity scores will be stratified into quintiles, and subsequent covariate balance will be reviewed graphically and with Mantel-Haenszel tests.

9.7.2 Main analysis using stratification

For the incident users of EMPAGLIFLOZIN along with their respective comparators, analysis will be performed using the "as-treated" (AT) approach. This corresponds to censoring individuals who discontinue use of the index drug, i.e. who either switch from the index drug to any other of the index drugs (EMPAGLIFLOZIN or DPP-4 inhibitor) during follow-up or who stop using the index drug. The AT approach is considering index periods. For each event of interest, ketoacidosis, severe urinary tract infections, volume depletion, and dehydration, crude and adjusted incidence rates per cohort will be described and compared by means of incidence rate ratios (IRR). Incidence rates will be reported as point estimates and 95% confidence intervals (CIs). Crude incidence rates will be adjusted per 1,000 person-years. Per cohort and, where appropriate per stratum and/or subgroup, the number of person-years is the sum of length of index periods of all patients. Time to first event occurrence will be compared by means of hazard ratios and their 95% confidence intervals.

IRRs and hazard ratios are analysed using stratification. Strata are defined by PS quintiles. IRRs are investigated by means of a stratified Mantel-Haenszel analysis, while hazard ratios are investigated by means of a Cox regression, if proportional hazards can be assumed.

9.7.3 Further analyses

9.7.3.1 Analyses on subsets of patients matched on PS

Propensity-score-matched cohorts will be derived for each comparison from the study base by matching patients who initiate empagliflozin with patients who initiate DPP-4 inhibitors using the greedy nearest-neighbor caliper matching method one by one without replacement. This approach may yield in patients of both cohorts not matching, while matched patients build a subset. Per cohort, baseline covariates and PS will be described for matched and non-matched patients. By means of standardized differences for baseline covariates balance will be assessed. As for the main analysis, data will be described in the subsets of matched patients only.

Hazard ratios for the outcomes will be estimated using Cox's PH model with time-varying covariates, if model pre-requisites are fulfilled. Hazard ratios will be presented along with 95% CIs.

9.7.3.2 Sensitivity and subgroup analyses

Secondary objectives are addressed by analyses of incidences during Ramadan periods only. Further analyses consider subgroups of resp. stratification by treatment complexity (mono vs. dual vs. triple therapy; different dose regimes), by insulin use at baseline and by calendar time of treatment initiation.

9.8 QUALITY CONTROL

All entries in the e-CRF and the existing codings will be stored in a database. The structure of the database is based on the division into sections and entry fields defined in the e-CRF. To improve and ensure data quality, data checks will be performed automatically in the e-CRF directly on electronic entry at the study site.
Plausible value ranges for numerical data entries and logical data and list entries will be filed in the e-CRF. The tests for consistency and completeness based on this will be performed during entry in the e-CRF. The validity of the recorded data will therefore be ensured by the validations incorporated in the documentation system, which highlight incorrect or implausible entries to the data entry clerk/doctor.
If corrections are necessary after the data are saved, these will be documented in an audit trail.
For the further quality assurance of the documented patient observations, a sample-based source data comparison will be performed on about 10% of the sites. An additional inspection/quality assurance check of this PASS can be performed in case of any deviation.

9.9 LIMITATIONS OF THE RESEARCH METHODS

There are several methodological challenges when conducting epidemiologic studies to evaluate the association between glucose-lowering medications and outcomes of interest among patients with diabetes. These challenges include, but are not limited to, changes in treatment in response to advancing diabetes or due to adverse effects of specific drugs and time-varying risk of an outcome depending on duration of exposure

Limitation including DKA sample size and Ramadan period

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor’s designees or by Institutional Review Board (IRBs) / Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator’s study-related files and correspondence, and the informed consent documentation of this study.

9.10.2 Study records

Case Report Forms (e-CRFs) for individual patients will be provided by the sponsor, either on paper or via remote data capture.

9.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the e-CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

For paper e-CRFs, the following data need to be derived from source documents:

- Patient identification (gender, date of birth)
- Patient participation in the study (substance, study number, patient number, date patient was informed)
- Dates of Patient's visits, including prescription of study medication
- Medical history (including study indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (SAEs) (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results (in validated electronic format, if available)
- Conclusion of Patient's Participation in the study

9.10.2.2 Direct access to source data and documents

The investigator / institution will permit study-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. e-CRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. US Food and Drug Administration (FDA)). The Clinical Research Associate (CRA) / Clinical Monitor Local (CML) and auditor may review all e-CRFs and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.1.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (to the extent applicable to the NIS setting and required by local regulations), Good Epidemiological Practice (GEP), Guidelines for Good Pharmacoepidemiology Practice (GPP), and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

The protocol of this regulatory requisite PASS will be submitted to Saudi FDA for review and approval. This study will be conducted in accordance with the SFDA guidelines of good pharmacovigilance practice version 2.0.
Boehringer Ingelheim Saudi Arabia will submit periodic reports as per SFDA guidelines of good pharmacovigilance practice version 2.0, and the final report to SFDA upon study completion. The periodic report for the final year will be substituted with the final report.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and Competent Authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CML/CRA) or Quality Medicine auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities <for EU>, *i.e. the CA*.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest (AESI)

The following are considered as AESIs:

Table 1: Clinical criteria for Adverse Event of Special Interest

Endpoint	**Definition**
Acute liver injury	Any the following criteria: • An elevation of AST and/or ALT ≥ 3-fold ULN combined with an elevation of bilirubin ≥ 2-fold ULN measured in the same blood draw sample. • An isolated elevation of AST and /or ALT ≥ 5-fold ULN irrespective of any bilirubin elevation
Decreased renal function	Creatinine value shows • a ≥ 2-fold increase from baseline and is above the upper limit of normal (ULN)
Metabolic acidosis, ketoacidosis and diabetic ketoacidosis (DKA)	Defined as a serious condition because of inability of body cells to get glucose as a source of energy, and subsequently, the body produces ketones as the result of burning fat for energy. DKA occurs because of a lack of insulin in the body, not enough food intakes in diabetic patients and insulin reaction (low blood glucose). It is characterized by high ketones levels, positive ketones in the urine and high pH levels. Specifically, for the SGLT2i induced DKA the blood glucose level may not be increased above 240 mg/dl.
Events involving lower limb amputation	This definition includes • amputation (i.e. resection of a limb through a bone), • disarticulation (i.e. resection of a limb through a joint) • and auto-amputations (i.e. spontaneous separation of non-viable portion of the lower limb). Not included in this definition are debridement (removal of callus or dead tissue), procedures on a stump (like stump revision, drainage of an abscess, wound revision etc.) and other procedures (e.g., nail resection or removal) without a concomitant resection of a limb (amputation or disarticulation).” Request to report each lower limb amputation as separate AE

ALT = alanine aminotransferase; ULN = upper limit of normal range.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs
The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason, the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the e-CRF from signing the informed consent onwards until the end of the study:

- all adverse event
-

All AES , including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**.
- A **plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of adverse event
The intensity of the AE should be judged based on the following:
Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate: Enough discomfort to cause interference with usual activity
Severe: Incapacitating or causing inability to work or to perform usual activities

Pregnancy:
In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well within the respective timelines.

Expedited Reporting of AEs and Drug Exposure During Pregnancy
The following must be reported by the investigator on the NIS AE form from signing the informed consent onwards until the end of the study:

Type of Report	Timeline
All **Serious Adverse Events** (SAEs) and **Adverse Event of Special interest**	immediately within 24 hours
All **AEs with fatal outcome**	immediately within 24 hours

All **non-serious Adverse Events**	7 calendar days
All pregnancy monitoring forms	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the NIS AE form.

Reporting of DKA cases:
An additional information will be requested with a targeted from.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate e-CRF pages and the NIS AE form.

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than the according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

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Include references with P, R, and S numbers here.

13.1 UNPUBLISHED REFERENCES

ra00656956 EMPAGLIFLOZIN® Company Core Data Sheet

C01678844-06 EMPAGLIFLOZIN Investigator's Brochure

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Documents listed in Annex 1 can be maintained separately from the study protocol. They should be clearly identifiable and provided on request. Write "None" if there is no document or list documents in a table as indicated below.

Number	**Document Reference Number**	**Date**	**Title**
<1>	<Number>	DD Month YYYY	<Text>
<2>	<Number>	DD Month YYYY	<Text>
<n>	<Number>	DD Month YYYY	<Text>

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

A copy of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (*ENCePP) Checklist for Study protocols available at website: encepp.eu/standards_and_guidances/index.html completed and signed by the main author of the study protocol should be included in Annex 2.*

The checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.

In question 9.5 of the Checklist, Revision 1:

"Study start" means "Start of data collection"
"Study progress" means "Progress report(s)"
"Study completion" means "End of data collection"
"Reporting" means "Final report of the study results"

ANNEX 3. ADDITIONAL INFORMATION

Additional annexes may be included if necessary.