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Statistical Analysis Plan (SAP)

Doument Date: 17APR2019 **Document Version: 1.0 Final**

Client Name	Protocol No	[redacted] Project Code
Boehringer Ingelheim International GmbH	1245.149	[redacted]

Protocol 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

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Table 1-1:Contact List

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Table 1-2: List of Abbreviations and Definition of Terms

ACE	Angiotensin-converting enzyme
AE	Adverse event
AESI	Adverse Event of Special Interest
ATC	Anatomic-therapeutic-chemical
BI	Boehringer Ingelheim
BMI	Body mass index
CI	Confidence interval
CRF	Case report form
DD	Drug dictionary
DPP-4	Dipeptidyl-peptidase 4
E-CRF	Electronic Case Report Form
EDC	Electronic Data Capture
GLD	glucose-lowering drug
GP	General practitioner
IR	Incidence rate
IRR	Incidence rate ratio
MedDRA	Medical dictionary for regulatory activities
MQ	Medical query
PH	Proportional hazards
PS	Propensity score
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System ®
SCCM	Society of Critical Care Medicine
SFDA	Saudi-Arabian Food & Drug Administration
SGLT2	Sodium-dependent glucose co-transporter 2
SI	Standard international

SOC	System organ class
T2DM	Type-2 Diabetes mellitus
UTI	Urinary tract infection
WHO	World Health Organisation

1 INTRODUCTION

This document details the analysis and data representations that are planned to be presented as part of the Boehringer Ingelheim study 1245.149. This is a non-interventional study at approximately 25 sites in Saudi Arabia with prospective data collection to examine the risk of ketoacidosis, severe urinary tract infections, volume depletion, and dehydration associated with the new use of EMPAGLIFLOZIN compared to the new use of Dipeptidyl peptidase-4 (DPP-4) inhibitors in a total of 1,500 type-2 diabetes mellitus (T2DM) patients. The treating physicians will mainly be general practitioners (GP) and/or specialists including endocrinologists, diabetologists and internists.

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.

2 OBJECTIVES AND END POINTS

This is a non-interventional study with new data collection.

2.1 Primary objective

The primary objective of this study is to estimate the incidence of

- Ketoacidosis
- Severe urinary tract infections (UTI)
- Volume depletion
- Dehydration

in T2DM patients initiating EMPAGLIFLOZIN compared with the incidence in T2DM patients initiating DPP-4 inhibitors.

The respective primary endpoints are incidences and occurrences of ketoacidosis, severe UTI, volume depletion and dehydration recorded as part of adverse event reporting and encoded according to MedDRA as defined in the Data Management Plan.

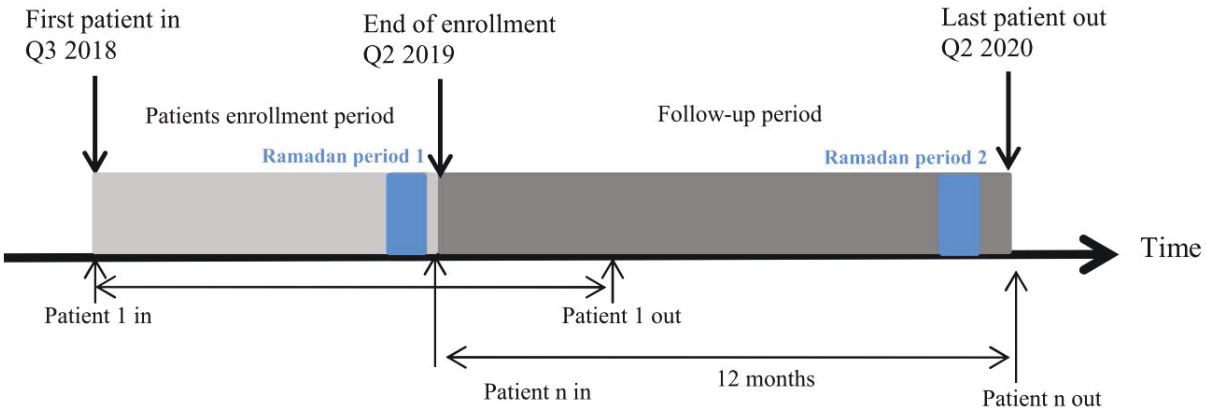
2.2 Secondary objectives

Further outcomes are estimates of the incidences of each primary outcome with respect to the Ramadan period (1st day of Ramadan to 29th day of Ramadan based on the Islamic Hijri calendar). Ramadan periods in 2019 and 2020 are given in Table 2-1 and visualized in Figure 2-1.

Table 2-1: Ramadan Time Periods 2019 and 2020

Ramadan Month 2019	May 5th, 2019, to June 4th, 2019, ± 1 to 2 days
Ramadan Month 2020	April 23rd, 2020, to May 23rd, 2020, ± 1 to 2 days

Figure 2-1: Study Time Flow including Ramadan Periods



The respective secondary endpoints are the same as the primary endpoints but restricted to incidences in the Ramadan periods. The follow-up period for each patient is one year.

3 STUDY OVERVIEW

The study will use an “incident users” design and compare new users of EMPAGLIFLOZIN with new users of DPP-4 inhibitors.

This study will be carried out by conducting successive surveys over the follow-up period.The investigator will be asked to record the information from the surveys 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.

The index date for each identified new user is defined as the date on which they receive the index prescription for EMPAGLIFLOZIN or DPP-4 inhibitors.

Patients are enrolled if at least 18 years of age at the index date, diagnosed with T2DM in Saudi Arabia, and who have not used other SGLT2 inhibitors during the previous 12 months. Patients are not enrolled if they have known hypersensitivity to EMPAGLIFLOZIN, the comparator DPP-4 inhibitors or any of their excipients, if EMPAGLIFLOZIN or the comparator DPP-4 inhibitor is contraindicated according SFDA approved label, or if they are on prescribed fixed-dose combinations of SGLT2 inhibitors with DPP-4 inhibitors.

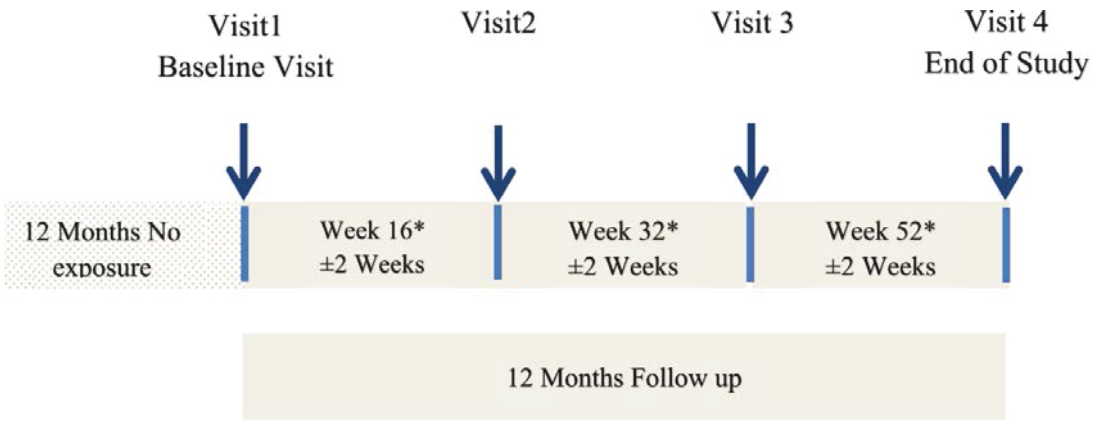
Follow-up will start the day after the index date and will continue until any of the following conditions are met:

- Death
- 12 months of follow-up
- specific exclusion criteria are met during follow-up
- 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)
- 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.

Four study visits will be held, at baseline, after 16, 32 and 52 weeks of follow-up.

Figure 3-1: Study Visits



'* from Visit 1

Table 3-1: Schedule of Visits

Assessment	Visit 1	Visit 2	Visit 3	Visit 4
Informed Consent	x			
Demographics	x			
Diagnosis	x			
Medical History	x			
HbA1c	x	*	*	*
Blood glucose level	*			
Other Laboratory/Renal Function	*			
Physical Examination (for vital signs)	x	*	*	*
Concomitant Medication incl. anti-hyperglycemic	x	#	#	#
Dose of Empagliflozin / DPP-4 inhibitor	x	#	#	#
Adverse Events		x	x	x
Study Completion Status		x	x	x

x = mandatory, * = if available, # = if changed

4 STATISTICAL METHODS

4.1 Scientific and Statistical Considerations of the Study Design

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.

Propensity scores based on information prior to and including the index date will be used to account for potential confounding.

4.2 Sample Size Rationale

The sample size of 1,500 patients is based on SFDA requirements. The aim is to achieve comparable group sample sizes of 750 patients each However given the real-world design of ths study this may not be possible.

4.3 Randomization and Unblinding Procedures

This is a non-interventional observational study. Patients are not randomly allocated to treatment. Randomization and unblinding procedures are not applicable.

4.4 General Principles

All individual collected and derived 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.

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.

Baseline (Visit 1) is defined as the last observation on or before the index date.

Let the *index period* define the time from index date to the end of treatment with either EMPAGLIFLOZIN or DPP-4 inhibitor, and the *follow-up period* the time from index date to the end of observation. The *index period during Ramadan* and the *follow-up period during Ramadan*, respectively, are the subperiods of index and follow-up periods, respectively, that will fall in the months of Ramadan as defined in Table 2-1 above, where June 6th 2019 and May 25th 2020 are assumed as the end of Ramadan for the two study years.

Durations of periods, time spans between visits and other times since the index date will be individually derived in days.

4.5 Datasets to be Analyzed

All patients fulfilling all inclusion criteria and none of the exclusion criteria will be evaluated in an Enrolled Set.

Inclusion criteria are:

- diagnosis with T2DM,
- ≥18 years of age at index date,
- initiation of EMPAGLIFLOZIN or DPP-4 inhibitor treatment according to the local label and at the discretion of the treating physician,
- signed informed consent form.

Exclusion criteria are:

- use of SGLT2 inhibitors during the previous 12 months,
- known hypersensitivity to EMPAGLIFLOZIN, the comparator DPP-4 inhibitors or any of their excipients,
- contraindication of EMPAGLIFLOZIN or the comparator DPP-4 inhibitor according SFDA approved label, and
- prescribed fixed-dose combination of SGLT2 inhibitors with DPP-4 inhibitors.

The propensity score analysis will lead to the creation of a Matched Set comprising a subset of subjects in the Enrolled Set (see section 4.9.3). This dataset will be used for additional analysis.

Frequencies of patients included in and excluded from analysis sets will be given.

4.5.1 Groups and subgroups

Patients are grouped according to the exposure to either EMPAGLIFLOZIN or DPP-4 inhibitors. Data will be analysed per group. DDP-4 inhibitors used include sitagliptin, saxagliptin, linagliptin, vildagliptin, and alogliptin.

All tables will show results per group (EMPAGLIFLOZIN or DPP-4 inhibitors) and for all patients in the analysis set. Additionally, selected tables will show results in subgroups for patients according to their metformin status, namely, whether or not they use metformin fixed combination therapy . Further subgroups are defined by mono, dual or triple therapy with glucose-lowering drugs (GLD) (the treatment complexity status), and by insulin use at baseline (the insulin status).

4.6 Statistical Hypotheses

If not otherwise specified, the level of significance is set to 0.05. All statistical tests will compare the treatment groups, EMPAGLIFLOZIN versus DPP-4 inhibitors, for difference. The null hypothesis is of no difference versus the two-sided alternative hypothesis which hypothesizes a difference between groups.

4.7 Analysis Parameters

All collected and derived individual data will be listed. Any derivations are described below. Parameter definitions are given. Summary tables and figures will be presented for the following data modules in all patients of the Enrolled Set. Analysis details are given below. On selected analysis parameters, summary tables and figures will also be prepared for the Matched Set.

4.7.1 Diagnosis and Family History of T2DM

The duration of T2DM will be determined as the time from date of diagnosis to index date in months.

Details of diagnosis will be listed and described per group by means of summary tables.

Details of diagnosis include

- Duration of disease in months, as the time from date of diagnosis to index date, calculated as the time span in days devided by 365.25/12,
- T2DM-related complication (retinopathy, neuropathy, nephropathy)
- Family history of T2DM. (yes/no)
- Insulin use (yes/no)
- HbA1c
- Fasting blood glucose level
- Treatment complexity (single,dual,triple)

4.7.2 Demographic and Other Characteristics

Demographic and other baseline characteristics will be listed and described per group by means of summary tables.

Demographic and other baseline characteristics include

- Gender,
- Age at index date in years, as the time from date of birth to index date,
- Age category (<30 years, 30 to 64 years and >64 years),
- Medical history (see below),
- Baseline laboratory test results, if available:, complete blood count, oral glucose tolerance test, ketones level, amylase, lipase, arterial blood gas, pH, bicarbonate, lipid profile tests, blood urea nitrogen, liver tests, International Normalized Ratio (INR) for prothrombin time,
- Renal function (within the last two months): Serum creatinine, eGFR, urine ACR,
- Physical examination at baseline: sBP (mmHg), dBP (mmHg), pulse rate (beats/min), weight (kg), height (cm), BMI (kg/m^2),
- Previous (within six months) and concomitant use of anti-hyperglycaemic agents at baseline,
- Previous (within one month) and concomitant medication at baseline.

Relevant medical history will be captured along with the start and end date of any condition and its status at enrollment (ongoing versus not ongoing). The medical history terms will be coded using the MedDRA dictionary, version 21.1. A table presenting the number and percentage of patients reporting medical history with respect to the system organ class (SOC) and preferred terms will be presented. Another such table will present the same for the subset of concomitant diseases ongoing at enrollment, i.e., at index date.

4.7.3 Exposure

Patients either receive EMPAGLIFLOZIN or a DPP-4 inhibitor, they may or may not receive respective fixed combinations with metformin and they may or may not combine the treatment with other GLDs.

To describe exposure, the following parameters will be derived:

- Duration of treatment as the length of the index period in days
- Number of interruptions of EMPAGLIFLOZIN or a DPP-4 inhibitor intake

- Extent of exposure as duration of treatment minus the number of days with interruptions
- Initial dose of EMPAGLIFLOZIN or a DPP-4 inhibitor
- Final dose of EMPAGLIFLOZIN or a DPP-4 inhibitor
- Proportion of subjects on metformin fixed-combination
- Proportion of subjects on mono, dual or triple therapy with other GLDs
- Proportion of subjects with insulin intake
- Proportion of subjects still on EMPAGLIFLOZIN or the DPP-4 inhibitor at end of study
- Proportion of subjects who discontinued EMPAGLIFLOZIN or the DPP-4 inhibitor before end of study
- Proportion of subjects still on EMPAGLIFLOZIN or the DPP-4 inhibitor at end of study or who discontinued EMPAGLIFLOZIN or the DPP-4 inhibitor no more than 30 days before end of study
- Proportion of subjects who discontinued EMPAGLIFLOZIN or the DPP-4 inhibitor 31 to 120 days before end of study
- Proportion of subjects who discontinued EMPAGLIFLOZIN or the DPP-4 inhibitor more than 120 days before end of study

The exposure parameters will be described by frequency and summary tables by group. Duration of treatment and extent of exposure will be evaluated as continuous count of number of days and in categories of 1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days and more than 360 days, respectively.

4.7.4 Adverse Events

All adverse events in patients who take at least one dose of EMPAGLIFLOZIN or DPP-4 inhibitor will be reported, encoded and categorized according to MedDRA version 21.1 and analysed. Relevant BIcMQs will be considered. Specific adverse events to be evaluated in this study are detailed in section 4.7.5. Other adverse events of special interest (AESI) as listed in Study Protocol Section 11.1 will also be evaluated.

All the information collected in the AE form in the CRF and the SOC and preferred term corresponding to each reported term will be presented in listings.

Incidences will be summarized and displayed by System Organ Class and preferred term per period (see section 4.4) for:

- all AEs,

- AEs by relationship to medication (EMPAGLIFLOZIN or DPP-4 inhibitor)
- SAEs
- AESIs.

The summary tables will display the number and percentage of patients experiencing the respective event at least once as well as the number of occurrences. Percentages will be calculated with respect to the total number of patients in the Enrolled Set. If an event is reported more than once for a patient, the incidence of the strongest relationship to medication will be counted in the calculation of percentages (i.e. so each patient is only counted once for preferred term).

4.7.5 Ketoacidosis, severe UTI, depletion and dehydration

As main endpoints, ketoacidosis, severe UTI (namely pyelonephritis and urosepsis), volume depletion and dehydration, will be derived from corresponding AE reporting. Crude and treatment-adjusted incidence rates will be presented by group and period, together with incidence rate ratios of EMPAGLIFLOZIN relative to DPP-4 inhibitor, as point estimates and with 95% confidence limits. Treatment-adjusted incidence rates are defined as crude incidence rates per 1,000 person-years. Per group, and, where appropriate, per stratum and/or subgroup, the number of person-years is the sum of length of index periods of all respective patients.

For each endpoint, the time from index date to first occurrence in days is determined. If the endpoint does not occur for a patient, the time is right-censored by the duration of the respective period, index period or follow-up period. By group, times to first occurrence will be described by means of Kaplan-Meier estimates with 95% confidence limits and, where appropriate, median times with 95% confidence limits.

Crude and treatment-adjusted incidence rates and respective incidence rate ratios will be described in summary tables by group and period, and per period in subgroups by metformin status, GLD status and insulin status, respectively. Ratios are defined as Empagliflozin to DPP-4 inhibitors.

4.7.6 Concomitant medication

Concomitant medications are defined as any medication other than Empagliflozin and DPP-4 inhibitors taken during the study. This includes any medication that started prior to enrollment,

but continued during the study, as well as medication that started after enrollment, but continued at the end of study.

Prior medications are defined as any reported medication that started prior to enrollment, whether stopped prior to enrollment or continued.

The prior and concomitant medications reported will be coded using WHO-DD in its 2020 version and summarized by ATC classes.

Frequencies of patients with at least one intake of prior medication, concomitant medication and concomitant medication at index date, respectively, will be presented in summary tables by ATC levels 1, 2 and 4.

4.7.7 HbA1c and Other Laboratory Tests

HbA1c will be described by summary tables per visit. Measured values in SI units as well as changes from baseline will be summarized if appropriate.

Other laboratory tests at baseline will be described by summary tables in SI units.

4.7.8 Completion Status and Discontinuation

A frequency table will describe the rate of subjects who completed or discontinued, and by reason of discontinuation. In a summary table, the length of follow-up period, i.e., the duration of observation, will be evaluated as continuous count of number of days and in categories of 1 to 30 days, 31 to 90 days, 91 to 180 days, 181 to 360 days and more than 360 days, respectively.

4.8 Handling of Missing Data

Data will be analyzed as reported. Missing data will not be replaced or imputed. Outlying values, if confirmed by site on data clarification, will be analyzed as reported.

Note that if specific endpoints (AEs i.e. ketoacidosis, volume depletion, dehydration serious UTI) are not reported for a patient in the AE section of the CRF it will be assumed that they did not experience that event.

4.9 Analyses

For descriptive analysis of parameters, see section 4.7 above. In the following, analysis of the endpoints is described in detail.

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 will be estimated. Hence, the following is applied to each of the four outcomes of interest.

The endpoints will be analysed in the index period (primary), in the index period during Ramadan (secondary), in the follow-up period and in the follow-up period during Ramadan. [redacted]

Estimation of propensity scores

In a preparatory step, for each patient, propensity scores (PS) will be estimated by means of logistic regression, estimating the likelihood of a patient receiving Empagliflozin based on prior and baseline confounders predictive of treatment. The statistical model will be built by a selection process optimizing the goodness of fit.

At first, the relationship between treatment (EMP, DPP-4 inhibitor) and all potential clinical confounder candidates will be tested in bivariate analyses. Based on the type of the candidate, Fisher's exact tests or Student's t-tests will be applied [Heiberger 2015]. In case of distributional constraints, χ^2 tests or Mann-Whitney U tests may be alternatively applied, respectively.

Clinically relevant confounder candidates include age, gender, body mass index (BMI), blood pressure, fasting blood glucose level at baseline, and baseline HbA1c, if available, comorbidity indicators like 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, genital defects, urinary tract anatomical defects, laboratory measurements and relevant prior and concomitant medications at baseline. Relevant prior medications in the last 6 months and at baseline include insulin sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, glucagon-like peptide-1 receptors, antihyperlipidemics (statins, fibrates, niacin), antihypertensive agents (diuretics, ACE inhibitors, beta blockers), antipsychotic medications, corticosteroids, tacrolimus, glucagon, interferon,

albuterol, dopamine, dobutamine, terbutaline and ritodrine. However, candidates cannot be considered if unknown or missing in a significant number of patients.

If the p-value of bivariate analysis is lower than 0.25, confounder candidates will be included in an initial multivariate logistic regression model. By backward elimination, or other appropriate methods of model selection, the model will be optimized to yield a final model.

The resulting PS will be described by group by means of a summary table. The distribution of the PS will be plotted for the two treatment groups (EMP, DPP-4 inhibitors) to see whether there are any areas where there is no overlap. The estimates of treatment effect may not be reliable in areas where there is no overlap. The area with overlap is called the common support region. It may be necessary to remove subjects outside of the common support region (e.g. extreme tails of the PS distribution) before analysis.

The effect of the confounders in bivariate testing and in the initial and final models will be described by p-values.

PS-based Analysis

Based on those PS, the main analysis approach is stratification to control for confounders, [redacted]

The stratification will divide the entire study population into five groups by PS quintiles based on their PS value. Quintiles will be used for analysis if the number of patients are sufficiently balanced per group within strata and if the confounding covariates are balanced. Balance will be reviewed graphically and, depending on the scale of the covariate, by Mantel-Haenszel and other applicable tests of confounding covariates of the final model by strata. If, due to significantly low p-values from Mantel-Haenszel and other applicable tests, the balance based on quintiles is insufficient, the number of strata will be increased. Balance investigations will be repeated and the number of strata further increased until a reasonable degree of balance is achieved. It may also be necessary to remove patients from extreme tails of the PS distribution.

4.9.1 Analysis of Primary Endpoints

For each of the four target adverse events (DKA, volume depletion, dehydration, serious UTI) the primary endpoints are the incidence rates and times to first occurrence in the index period,

analysed within each PS-based stratum by logistic regression and proportional-hazards Cox regression, respectively. Time to first event occurrence will be compared using hazard ratios and their 95% confidence limits. The assumption of proportional hazards will be tested [Kleinbaum 2012].

Estimates for each stratum and respective variances will be averaged across strata to yield overall weighted estimates considering subclass weights [Austin 2010, Guo 2015].

The statistical analysis models will contain factors and covariates with a potential effect on the outcome. These may include the treatment-confounding candidates listed in section 4.9 above, and will include the season, i.e., the quarter of the calendar year of the index date, and other effects yet to be short-listed . Site may also be included as a candidate. variable.

4.9.2 Analysis of Secondary Endpoints

Secondary endpoints are the same as primary endpoints but in the index period during Ramadan. They are analyzed like the primary endpoints.

[redacted]

[redacted]

4.9.4 Analysis in Subgroups

Further analyses consider subgroups by treatment complexity status, by insulin use at baseline and by metformin status in a descriptive manner. That is, analyses as described above, will be repeated within subgroups.

4.10 Changes From Protocol-Specified Analyses

As planned per protocol, stratified Mantel-Haenszel analysis will be applied to evaluate incidence rates of each of the target AEs. [redacted]

5 LIST OF PLANNED TABLES, FIGURES AND LISTINGS

5.1 Tables

Table 5-1: Table of Content of Tables

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1	Analysis Sets
2	Durations, Completion and Discontinuation of Follow-up
3	Demography
4.1	Medical History
4.2	Concomitant Diseases at Index Date

5.1	Prior Medication
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15.23	Diabetic Ketoacidosis: Stratified PH Analyses of Time to First Occurrence in Index Period during Ramadan
15.24	Diabetic Ketoacidosis: Stratified PH Analyses of Time to First Occurrence in Follow-up Period
15.25	Diabetic Ketoacidosis: Stratified PH Analyses of Time to First Occurrence in Follow-up Period during Ramadan
16.1-25	same 25 outputs for severe UTI
17.1-25	same 25 outputs for volume depletion
18.1-25	same 25 outputs for dehydration

5.2 Figures

Table 5-2: Table of Content of Figures

No.	Title of the Figure
1.1	Crude Incidence Rates of Primary Outcomes in Index Period
1.2	Crude Incidence Rates of Primary Outcomes in Index Period during Ramadan
1.3	Crude Incidence Rates of Primary Outcomes in Follow-up Period
1.4	Crude Incidence Rates of Primary Outcomes in Follow-up Period during Ramadan
2.1	Treatment-adjusted Incidence Rates of Primary Outcomes in Index Period
2.2	Treatment-adjusted Incidence Rates of Primary Outcomes in Index Period during Ramadan
2.3	Treatment-adjusted Incidence Rates of Primary Outcomes in Follow-up Period
2.4	Treatment-adjusted Incidence Rates of Primary Outcomes in Follow-up Period during Ramadan
3.1	Time to First Occurrence per Primary Outcome in Index Period – Kaplan-Meier plot
3.2	Time to First Occurrence per Primary Outcome in Follow-up Period – Kaplan-Meier plot
4.1	Propensity Scores in Enrolled Set – Box plot by Group and Subclass
4.2	Propensity Scores in Matched Set – Box plot by Group and Subclass

5.3 Listings

Table 5-3: Table of Content of Listings

No.	Title of the Listing
1	Sites and Patients with Analysis Set Status
2	Dates, Visits, Dosage Changes and Continuation Status
3	Demography
4.1	Medical History - Details
4.2	Medical History - Coding
5	Physical Examination by Visit
6	History of T2DM and Complications
7	Inclusion/Exclusion Criteria
8	Study Treatment Details
9	HbA1c Measurements and other Laboratory Tests by Visit
10	Renal Function Tests
11.1	Adverse Events - Details

No.	Title of the Listing
11.2	Adverse Events – Medical Coding
12	Hospitalizations
13.1	Prior/Concomitant Medications - Details
13.2	Prior/Concomitant Medications - Coding
14	Completion/End of Study
15.1	Occurrences and Times to First Occurrence for Primary Outcomes
15.2	Propensity Scores

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Statistical Analysis Plan (SAP)

Client Name	Protocol No	[redacted] Project Code
Boehringer Ingelheim International GmbH	1245.149	[redacted]

Protocol 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

[redacted] and [redacted] Clinical Data Services; [redacted]	Signature	Date (DDMMMYYYY)
[redacted]	[redacted]	18APR2019

[redacted] Biostatistician, [redacted]	Signature	Date (DDMMMYYYY)
[redacted]		

Name (Client Biostatistician, [redacted]	Signature	Date (DDMMMYYYY)
[redacted]		

Medical [redacted] Saudi Arabia, Boehringer Ingelheim	Signature	Date (DDMMMYYYY)
[redacted] Medical [redacted]		

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17APR2019	**Final 1.0**

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Statistical Analysis Plan (SAP)

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[redacted]	[redacted]	18 APR 2019

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[redacted]		

Name (Client Biostatistician, [redacted]	Signature	Date (DDMMMYYYY)
[redacted]	[redacted]	23APR 2019

Medical [redacted] Saudi Arabia, Boehringer Ingelheim	Signature	Date (DDMMMYYYY)
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