Boehringer Ingelheim

Non-Interventional Study (NIS) Protocol

Document Number:	c39368586-02
BI Study Number:	1245-0228
BI Investigational Product(s):	Jardiance® (empagliflozin)
Title:	Comparative cardiovascular and renal effectiveness and safety of Empagliflozin and other SGLT2i in patients with type 2 diabetes (T2D) with and without baseline kidney disease in the United States
Brief lay title:	Evaluating comparative effectiveness of empagliflozin in patients with type 2 diabetes with and without chronic kidney disease
Protocol version identifier:	2.0
Date of last version of protocol:	10June2022
PASS:	No
EU PAS register number:	EUPAS45682
Active substance:	A10BK03 Empagliflozin
Medicinal product:	Jardiance®
Product reference:	NA
Research question and objectives:	The primary objective of this research study is to determine the cardiovascular and renal effectiveness and safety of empagliflozin compared to dipeptidyl peptidate-4 inhibitor (DPP4i) in patients with T2D in the 1. Overall cohort, 2. Patients with established kidney disease (DKD cohort), and 3. Patients without established kidney disease (non-DKD cohort).

	The secondary objective of this research study is to determine the cardiovascular and renal effectiveness and safety of any sodium glucose co-transporter-2 inhibitors (SGLT2i) compared to glucagon-like peptide-1 receptor agonists (GLP1RA) in patients with T2D, overall and by DKD status.
Country(-ies) of study:	United States of America
Author:	[redacted]
Marketing authorisation holder(s):	Boehringer Ingelheim International GmbH
Date:	26 May 2023

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ACD	All-Cause Death
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
AKI	Acute Kidney Injury
ASMD	Absolute Standardized Mean Difference
AT	As-Treated
BI	Boehringer Ingelheim
CA	Competent Authority
CCDS	Company Core Data Sheet
CDM	Common Data Model
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CV	Cardiovascular
DKD	Diabetic Kidney Disease
DMRP	Data Management and Review Plan
DPP4i	Dipeptidyl Peptidate-4 inhibitor
eCRF	Electronic Case Report Form
ED	Emergency Department
EHR	Electronic Health Record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESRD/ESKD	End Stage Renal (Kidney) Disease
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice

GLP1RA	Glucagon-like Peptide-1 Receptor Agonists
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
HF	Heart Failure
HR	Hazard Ratio
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IQR	Interquartile Range
IRB	Institutional Review Board
ITT	Intent-to-treat
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
PASS	Post-Authorization Safety Study
PCORnet	Patient Centered Outcomes Research Network
PS	Propensity Score
QC	Quality Control
SAE	Serious Adverse Event
SEAP	Statistical and Epidemiological Analysis Plan
SGLT2i	Sodium glucose co-transporter-2 inhibitors
SOP	Standard Operating Procedure
SSDC	Study Specific Data Characterization
T1D	Type 1 Diabetes Mellitus
T2D	Type 2 Diabetes Mellitus
UTI	Urinary Tract Infection

3. RESPONSIBLE PARTIES

The responsible parties, study investigators, and protocol authors are as follows:

1) [redacted]:
- [redacted] Investigator
- [redacted]: Co-Investigator
- [redacted] Biostatistician
- [redacted] Biostatistician
- [redacted]: Project [redacted]

2) Boehringer Ingelheim:
- [redacted]: NIS [redacted]

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Jardiance®			
Name of active ingredient: A10BK03 Empagliflozin			
Protocol date: 26 May 2023	**Study number:** 1245-0228	**Version/Revision:** 2.0	**Version/Revision date:** 26 May 2023
Title of study:	Comparative cardiovascular and renal effectiveness and safety of Empagliflozin and other sodium glucose co-transporter-2 inhibitors in patients with type 2 diabetes with and without baseline kidney disease in the United States		
Rationale and background:	While clear renal and cardiovascular (CV) benefits of empagliflozin have been demonstrated in randomized clinical trials [P15-09840], the effectiveness of this therapy in direct comparison to other anti-hyperglycemic therapies has not been shown among patients with diabetic kidney disease (DKD). Understanding the real-world clinical impact of empagliflozin in this high-risk population is critical to elucidate this medication's effect on clinical care and outcomes. Overall, we aim to use a large, national network of electronic health record (EHR) data to determine the following in a real-world population: 1) Characteristics of patients with T2D, both with and without DKD, who have been initiated on empagliflozin or any sodium glucose co-transporter-2 inhibitors (SGLT2i) compared to those who have been initiated on dipeptidyl peptidate-4 inhibitor (DPP4i) or glucagon-like peptide-1 receptor agonists[1] (GLP1RA) 2) Renal and CV effectiveness of empagliflozin compared with DPP4i and SGLT2i compared with GLP1RA evaluated up to 24 months after treatment initiation 3) Safety of empagliflozin compared with DPP4i and any SGLT2i compared to GLP1RA evaluated up to 24 months after treatment initiation		
Research question and objectives:	The primary objective of this research study is to determine the cardiovascular and renal effectiveness and safety up to 24 months after initiation of empagliflozin compared to DPP4i in patients with T2D in the 1. Overall cohort, 2. Patients with established kidney disease (DKD cohort) at baseline, and 3. Patients without established kidney disease at baseline (non-		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Jardiance®			
Name of active ingredient: A10BK03 Empagliflozin			
Protocol date: 26 May 2023	**Study number:** 1245-0228	**Version/Revision:** 2.0	**Version/Revision date:** 26 May 2023

	DKD cohort).
Study design:	This will be a non-interventional study (NIS) using existing data from 20+ US health systems that have mapped their EHR data to the PCORnet Common Data Model [*R21-4494*]. The study period will be from 1 Jan 2014 through 31 December 2021, which includes data after the start of the COVID-19 pandemic. There will be an assessment of COVID-era data for quality purposes and a sensitivity analysis excluding data from March 2020 (the assumed beginning of COVID in the US) to the end of study period will be performed. The primary aim of the study will include patients with T2D who initiate use of empagliflozin or DPP4i without prior use of either drug [class]. The analyses of all outcomes will compare patients with T2D initiating empagliflozin to patients with T2D initiating DPP4i. The secondary aim of the study will be to examine cardiovascular and renal effectiveness and safety associated with initiation of any SGLT2i compared to GLP1RA in patients with T2D who initiate treatment without prior use of either drug class.
Population:	The analysis will include adults (≥18 years) with T2D with or without kidney disease in the US. To study real-world treatment patterns, the study population will include a broad spectrum of patients initiating empagliflozin or any SGLT2i, DPP4i or GLP1RA. The following inclusion and exclusion criteria will be used for each two-arm comparison: Inclusion criteria: - Patients ≥18 years old, - Having a diagnosis of T2D within 12 months prior to the index date based on ICD-9 and -10 codes and other available data, - Record of 1+ prescription for empagliflozin, any SGLT2i, any DPP4 inhibitor, or any GLP1RA use between 1 January 2015 and 31 December 2020, and - No record of any prescription for the drugs being compared

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Jardiance®			
Name of active ingredient: A10BK03 Empagliflozin			
Protocol date: 26 May 2023	**Study number:** 1245-0228	**Version/Revision:** 2.0	**Version/Revision date:** 26 May 2023

	during the 12 months preceding the index date, i.e., o For the primary comparison of initiation of empagliflozin versus DPP4 inhibitors, patients will not have any prescription for empagliflozin/any SGLT2i or DPP4 inhibitors during the preceding 12 months. o For the comparison of initiation of SGLT2i versus GLP1RA, patients will not have any prescription for SGLT2i or GLP1RA during the preceding 12 months. Exclusion criteria: - Aged <18 years on the first prescription date of the qualifying prescription, - Pre-existing diagnosis of Type 1 diabetes (T1D) during the 12 months before the index date, - Having a disqualifying diagnosis during the 12 months before the index date, defined as having at least one of the following: estimated glomerular filtration rate (eGFR) <30, dialysis, polycystic kidney disease or a kidney transplant, - <12 months of available data before the index date, and/or no complete history of drug prescriptions/or other records of drug use during this period, defined as not having at least 1 ambulatory visit and at least 1 medication prescription during the preceding 12 months, and - Missing or ambiguous data on serum creatinine in the preceding 12 months.
Variables:	<u>Exposure variables will include:</u> • Initiation of empagliflozin, GLP1RA, DPP4 inhibitors or any SGLT2i for the treatment of T2D <u>Outcomes (evaluated through 24 months after index date):</u> Primary effectiveness outcomes: • Composite of a 40% decline in eGFR, incident ESRD, or all-cause death (ACD)

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Jardiance®			
Name of active ingredient: A10BK03 Empagliflozin			
Protocol date: 26 May 2023	**Study number:** 1245-0228	**Version/Revision:** 2.0	**Version/Revision date:** 26 May 2023
	Secondary effectiveness outcomes: • Individual renal events: 40% decline in eGFR, incident ESRD, dialysis, and kidney transplant • Hospitalizations for cardiovascular events: heart failure (HF), HF+ACD, myocardial infarction+stroke+coronary revascularization+ACD, myocardial infarction+stroke+ACD • ACD Secondary safety outcomes: • Diabetic ketoacidosis • Severe hypoglycaemia • Urinary tract cancer • Acute kidney injury (AKI) that requires dialysis • Genital mycotic infection • Severe urinary tract infections <u>Covariates:</u> Several baseline patient characteristics will be captured in the 12 months prior to the index date. Covariates that will be included as covariates in the propensity scores (PS) model include (not are not limited to): • Demographics (age, sex, race/ethnicity, BMI, quarter and year of incident prescription, smoking status) • Comorbidities: history of heart failure, history of CV events (MI, stroke, PCI, CABG, PAD), hypertension • Prior/concomitant use of other glucose lowering agents • Prior/concomitant use of other medications e.g., cardiovascular agents (ACE/ARB, beta blocker, ARNi, statin) and diuretics • Relevant lab test results, e.g., eGFR, HbA1c, HDL-c, etc. Note: See Section 9.3.3 for complete list of covariates		
Data sources:	This study will utilize high-quality renal function laboratory data available in medical electronic health records from approximately 20		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Jardiance®			
Name of active ingredient: A10BK03 Empagliflozin			
Protocol date: 26 May 2023	**Study number:** 1245-0228	**Version/Revision:** 2.0	**Version/Revision date:** 26 May 2023

	health systems in the US that have mapped their data to the PCORnet Common Data Model (CDM). Sites meeting PCORnet data curation quality checks will be eligible to participate in this study. Sites will be approached for participation in this study based on an initial feasibility assessment to determine the extent and completeness of key data elements (renal laboratory data, prescription data, relevant medical diagnoses, and data from both inpatient and outpatient encounters). Death data will be ascertained from site records and augmented with de-identified encrypted linkage to external sources, which includes reported deaths from the government and commercial obituaries using Datavant Software.
Study size:	A sample size of N=7,600 per group with median follow-up duration of 18 months will provide 80% power to detect a hazard ratio of 0.80, assuming an incidence rate of 30 per 1,000 patient years for the primary composite renal outcome in the reference cohort.
Data analysis:	The index date in this study is defined as the date of the first recorded order for a qualifying prescription as a new user. Patients are required to have at least 1 ambulatory visit and at least 1 medication prescription in the 12 months prior to initiation of empagliflozin or a comparator drug (the look-back period). The look-back period includes the index date. The main analyses of this study will utilize a modified As-Treated (AT) approach and an Intention-to-Treat (ITT) approach will be used as a sensitivity analysis for the primary and secondary comparisons of the primary outcome. Follow-up starts from the day after the index date until the first qualifying event has been met: • First occurrence of outcome of interest • Death • 2 years following the index prescription • End of query specific study period (December 31, 2021) • Empagliflozin user starts a DPP4i or other type of SGLT2i, or if a DPP4i user starts any SGLT2i o SGLT2i user starts a GLP1RA, or a GLP1RA user starts any SGLT2i

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Jardiance®			
Name of active ingredient: A10BK03 Empagliflozin			
Protocol date: 26 May 2023	**Study number:** 1245-0228	**Version/Revision:** 2.0	**Version/Revision date:** 26 May 2023

- No observed prescriptions for the index drug within 1 year (+30 days) from the last observed prescription

The primary analysis will be performed using overlap weighting to balance covariates across the two treatment arms (empagliflozin vs DPP4i) and Cox proportional hazards modelling to determine the effect of drug on outcomes. To create the overlap weights, the following will be performed:

For each two-arm study comparison and within the DKD and non-DKD subgroups separately, propensity score models will be built using a logistic LASSO model with the covariates of interest and all subgroup by covariate pairwise interactions. The outcome of interest is treatment group, with empagliflozin [or any SGT2i] as the treatment of interest and DPP4i [or GLP1RA] as the reference group. The variables/interactions that are remaining in the LASSO model are refit to a standard logistic regression and the resulting predicted probability for each patient is considered the PS. For patients on the reference treatment, the overlap weight is the same as the PS. For patients on the treatment of interest, the overlap weight is 1-PS. No trimming is required due to the PS weights being bounded between 0 and 1. Distributions of covariates in the DKD and non- DKD groups and further within subgroups of interest will be assessed using standardized mean differences. Absolute standardized mean differences will be visually depicted using the CONNECT-S plot.

For each outcome, incidence rates (number of events per 1000 PY of follow-up), hazard ratios, and corresponding 95% confidence intervals (CI) will be presented. Hazard ratios and CI will be calculated using weighted Cox proportional hazards models. For the AT analysis, if an empagliflozin or DPP4i user initiates a GLP1RA during the follow-up period, this will be adjusted for in the comparison of empagliflozin and DPP4i (and similarly for users initiating a DPP4i).

Analyses will be performed overall and within DKD subgroups.

A sensitivity analysis will be performed using propensity score

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Jardiance®			
Name of active ingredient: A10BK03 Empagliflozin			
Protocol date: 26 May 2023	**Study number:** 1245-0228	**Version/Revision:** 2.0	**Version/Revision date:** 26 May 2023
	matching in place of overlap weighting. Another sensitivity analysis will be performed excluding data available from March 2020 to the end of the study period to reduce the impact of the pandemic. A sensitivity analysis for the primary efficacy comparison will be performed where eGFR decline requires ≥1 measurement during follow-up (instead of ≥2). Given this is a retrospective study utilizing EHR data from multiple sites, the protocol-specified analyses may need to be modified based on overall data collection completeness (data latency) and final cohort sample sizes.		
Milestones:	- Final protocol and SEAP: Q2 2022 - ENCEPP registration: After finalization of the study protocol (Q2 2022) - Contracts executed with sites: Q1 2022 - Data collection via distributed query: Q2 2022 - Final report: Q4 2023 - Manuscript submission: Q4 2023		

5. AMENDMENTS AND UPDATES

Number	Date	Section of the study protocol	Amendment or update	Reason
1	26 May 2023	Abstract 8.0 Research questions and objectives 9.1 Study design 9.2.2.2 Flowchart 9.3.1 Exposures	Removal of analyses involving comparison of empagliflozin vs GLP1RA.	Phase 1 analyses indicated differences in treatment exposure between patients prescribed empagliflozin compared to those prescribed GLP1RAs (i.e., greater proportion of patients prescribed 4+ prescriptions observed for GLP1RA over follow up)
			Timelines/milestones extended	Update protocol to reflect study progress at time of amendment
			EU PASS Register Number added	Number not available at time of initial protocol approval
		9.3.2.2 Outcomes	Added study outcome	The composite outcome of MI + stroke+all-cause death+ cardiovascular revascularization was previously in the protocol but the composite MI+stroke +all-cause death was added

Number	Date	Section of the study protocol	Amendment or update	Reason
		9.7.3.0 Sensitivity analysis	Addition of acute HHF codes as a sensitivity analysis	The initial broader codelist for HHF will be performed but a sensitivity analysis only including HHF that indicate acute HF will be examined.

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	June 2021
Start of data collection	May 2022
End of data collection	July 2022
<Registration in the EU PAS register>	June 2022
Final results ready	Q4 2023
Final report of study results:	Q4 2023

7. RATIONALE AND BACKGROUND

The global prevalence of diabetes has increased nearly 4-fold in the last forty years and this increase is projected to continue [R21-4492]. Diabetic kidney disease (DKD) affects 30-40% of persons with diabetes and is the leading cause of end-stage renal disease (ESRD) in the Unites States [P18-00615, R19-1661].] The development of DKD substantially increases the risk of mortality for persons with diabetes [R13-0685].] Empagliflozin and other sodium-glucose cotransporter 2 inhibitors (SGLT2i) have emerged as the first promising advance in the care of DKD for nearly two decades. While kidney and cardiovascular outcomes trials have demonstrated clear cardiorenal benefit for empagliflozin and SGLT2i above standard care and renin-angiotensin-aldosterone axis blockade [P15-09840, P16-06807, R19-1356, R21-1080],] no definitive study has compared the effectiveness of empagliflozin to other anti-hyperglyemic therapies. Since some of these therapies have putative cardiorenal benefits and risks [R18-1139, R17-1732, R21-4493], a direct comparison of empagliflozin and SGLT2i to these therapies is imperative.

In addition, the EMPRISE US study [P21-10532] used diagnostic coding from claims data to identify incident cases of end stage renal disease (ESRD) as the main renal outcomes and assessed the comparative effectiveness of empagliflozin vs DPP4 inhibitors. The current study builds upon the EMPRISE US study by also including key aspects of laboratory data that allow for assessment of eGFR-based renal outcomes and analyses of CKD cohorts defined by eGFR levels. This is a relevant adaptation to the EMPRISE US study methodology in that use of eGFR assessments of renal function are a more sensitive approach for categorizing CKD stages and monitoring changes in renal function over time. If feasible, this study will also include comparisons of risk for study outcomes between empagliflozin or SGLT2i compared to both DPP4 inhibitors and GLP1RAs. GLP1RA was not included in the EMPRISE studies as a comparison group.

8. RESEARCH QUESTION AND OBJECTIVES

The primary purpose of this research study is to determine the cardiovascular and renal effectiveness and safety of empagliflozin compared to DPP4i in patients with T2D in the

- Overall cohort,
- Patients with established kidney disease (DKD cohort), and
- Patients without established kidney disease (non-DKD cohort).

The secondary purpose of this research study is to determine the cardiovascular and renal effectiveness and safety of any SGLT2i compared to GLP1RA

9. RESEARCH METHODS

9.1 STUDY DESIGN

This will be a non-interventional comparative effectiveness and safety study, using existing (secondary) data from up to 20 US health systems that have mapped their electronic health record data to the PCORnet Common Data Model (CDM). The study period will be 1 January 2014 through 31 December 2021, which includes data during the COVID-19 pandemic. There will be an assessment of COVID-era data for quality purposes, and we will perform a sensitivity analysis excluding all data available from March 2020 to the end of the study period.

The primary objective of the study will include patients with T2D who initiate use of empagliflozin or DPP4i without prior use of either drug [class]. The primary analysis will compare patients with T2D initiating empagliflozin to patients with T2D initiating DPP4i.

The secondary objective of the study will include an additional cohort of patients: those with T2D who initiate use of any SGLT2i or GLP1RA without prior use of either drug class.

Propensity score weighting (overlap weighting [R20-1964, R21-4495] will be used to balance covariates between two treatment groups in each comparison (empagliflozin vs DPP4i; SGLT2i vs GLP1RA). With overlap weighting, the resulting reweighted sample targets the subpopulation of patients with the most overlap in covariates across the two treatment groups. Patients in this subpopulation have substantial probability to be assigned to either treatment of interest, and therefore represent patients for whom there is clinical equipoise for treatment assignment. Propensity score models will be developed, and the reweighted populations will be assessed to ensure cross-treatment group covariate balance within both the DKD and non-DKD subgroups, as well as for the overall cohorts using methods of Yang et al [R21-4497]. Additional details about propensity score modeling and reweighting are provided in the section on Data Analysis.

Study feasibility will be evaluated after data collection has occurred. If the final sample size does not meet the required sample size for 80% power, the planned sensitivity and subgroup analyses will be removed from the final study report. The primary analyses will still be assessed but in an exploratory capacity.

9.2 SETTING

9.2.1 Study sites

This study will utilize high-quality renal function laboratory data available in medical electronic health records from approximately 20 health systems in the US that have mapped their data to the PCORnet Common Data Model (CDM). Sites meeting PCORnet data curation quality checks will be eligible to participate in this study.

9.2.2 Study population

The analysis will include adults (≥18 years) with type 2 diabetes with or without kidney disease in the US. To study real-world treatment patterns, the study population will include a broad spectrum of new users of empagliflozin, SGLT2i, DPP4i or GLP1RA. The following inclusion and exclusion criteria will be used for each two-arm comparison:

9.2.2.1 Inclusion criteria

Inclusion criteria:

- Patients ≥18 years old,
- Having a diagnosis of type 2 diabetes in 12 months before the index date (defined as the date of initiation of empagliflozin or GLP1RA or DPP4i, based on the cohort evaluated), based on ICD-9 and -10 codes and other available data (see SEAP for details),
- Record of prescription for empagliflozin, any SGLT2i, any DPP4 inhibitor, or any GLP1RA use between 1 January 2015 and 31 December 2020, and
- No record of any prescription for the drugs being compared during the 12 months + 30-day grace preceding the index date period, i.e.,
    - For the primary comparison of initiation of empagliflozin versus DPP4i, patients will not have any prescription for empagliflozin/any SGLT2i or DPP4i during the preceding 12 months + 30-day grace period.
    - For the comparison of initiation of SGLT2i versus GLP1RA, patients will not have any prescription for SGLT2i or GLP1RA during the preceding 12 months + 30-day grace period.

9.2.2.2 Exclusion criteria

Exclusion criteria:

- Aged <18 years on the first prescription date of the qualifying prescription,
- Pre-existing diagnosis of T1DM during the 12 months before the index date,
- Having a disqualifying diagnosis during the 12 months before the index date, defined as having at least one of the following: eGFR<30, dialysis, polycystic kidney disease or a kidney transplant,
- <12 months of available data before the index date, and/or no complete history of drug dispensations/other records of drug use during this period, defined as not having at least 1 ambulatory visit and at least 1 medication prescription during the preceding 12 months, and
- Missing or ambiguous data on serum creatinine in the 12 months prior to the index date or sex.

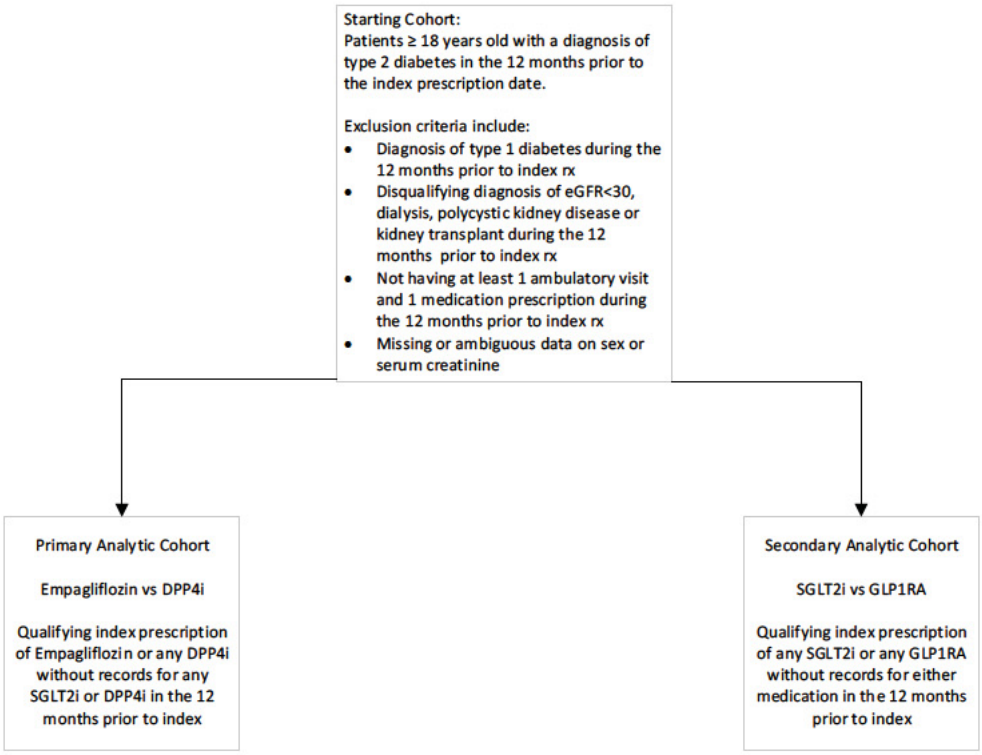

Figure 1 Consort diagram of study population, the application of inclusion and exclusion criteria, and the resulting study cohorts

9.2.3 Study visits

Patients will enter the study cohort on the date of their incident prescription for empagliflozin, other SGLT2i or comparator drug (baseline date) during 2014 – 2020. Baseline data will be determined from records at the baseline encounter, and from other health system encounters up to 12 months prior to baseline (see table below for specific look back periods). Follow-up data (relevant medication prescriptions, measurements, and records for determining outcomes) will be collected until 31 December 2021 (study end date), but outcomes will be censored at 2 years after index date or end of data collection, if earlier.

Table 1 Timing of patient characteristics, clinical information, and follow-up data relative to baseline

	1 Year Prior to Baseline	Baseline	+/- 3 months from baseline	+/- 30 days from baseline	Post baseline
Demographics		X			
Medication Prescriptions	X	X			X
Medical History	X				
Labs			X		X
Vitals				X	
Hospitalization Events					X
Death					X

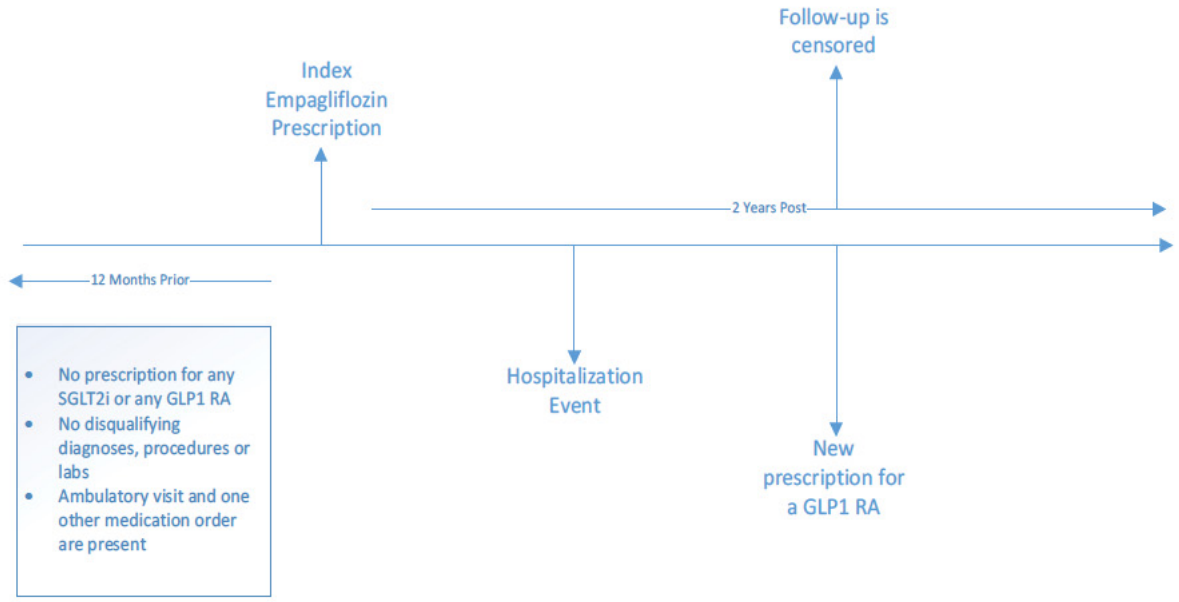

Figure 2 Example exposure period from lookback (12 months pre-index prescription) to the post-index censoring event for a patient in the empagliflozin cohort. Example includes an event of interest (hospitalization) and the censoring time point for new GLP1RA prescription.

9.2.4 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 enrollment goals overall or at a particular study site
2. Emergence of any methodological, effectiveness, or safety information that could significantly affect continuation of the study, or any other relevant administrative reasons.
3. Violation of Good Pharmacoepidemiology Practice (GPP), the study protocol, or the contract by a study site, investigator or research collaborator, disturbing the appropriate conduct of the study

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

9.3 VARIABLES

9.3.1 Exposures

Primary exposure (see Statistical and Epidemiological Analysis Plan for applicable drug codes):

- Main comparison:
    - Incident prescription order of empagliflozin [ATC codes: A10BK03, A10BD20] without prior use of any SGLT2i or DPP4 inhibitors
    - Incident prescription order of any DPP4 inhibitor without prior use of any DPP4 inhibitor or any SGLT2i
- Secondary comparison:
    - Incident prescription order of any SGLT2i without prior use of SGLT2i or GLP1RA
    - Incident prescription order of any GLP1RA without prior use of any GLP1RA or SGLT2i

A modified As-Treated (AT) approach will be used for all analyses. Patients will be included in their incident prescription cohort with censoring occurring for the following reasons:

- Occurrence of outcome of interest
- Empagliflozin user has new prescription for a different SGLT2i during follow-up
- Empagliflozin [SGLT2i] user has new prescription for the comparator drug of interest during follow-up
- DPP4i or GLP1RA user has new prescription for any SGLT2i during follow-up
- No additional prescription for the incident drug has been written in the 1 year (+30 days) since the last observed prescription
- 2 years following index prescription
- End of study period

This modified approach will be used due to inconsistencies in the available prescribing data (e.g., number of fills, number of pills) and discontinuation dates across PCORnet healthcare sites and the fact that claims/fill data are not available in PCORnet to supplement the written orders. We will assume a patient is on their initial prescription unless the criteria above have been met.
To better understand potential limitations of this modified AT approach, a feasibility assessment will be performed once the initial data queries are performed to examine the extent of more detailed prescribing information (e.g., number of fills, number of pills, discontinuation dates) across participating healthcare sites. If feasibility is determined by the investigative team, sensitivity analyses will be performed including sites with more complete prescribing information examining all primary and secondary outcomes (See section 9.7.2).

The intention-to-treat (ITT) approach will be used as a sensitivity analysis for the primary and secondary comparisons of the primary outcome. In this ITT analysis, follow-up will not be censored when a patient switches to, or adds, treatment with a different agent.

Primary subgroup of interest: diabetic kidney disease (DKD)

- DKD will be defined using diagnosis codes and laboratory values based on records at the index encounter and from other health system encounters up to 12 months prior to index prescription. Analyses will be performed overall and within subgroups of DKD (DKD and no DKD at baseline).

9.3.2 Outcomes

Any outcome requiring at least 2 measurements meeting the event definition over a specified timeframe will have a date of event set to the date of the first measurement.

9.3.2.1 Primary renal effectiveness outcomes

Table 2 Primary outcome included in this study

Outcome	**Definition**
Composite outcome including 40% decline in eGFR Incident end-stage renal disease (ESRD) All-cause death	40% decline in eGFR: at least 2 measurements* during follow-up of at least a 40% decline relative to baseline separated by ≥ 28 days [R21-4243]. ESKD definition: at least 1 kidney transplant or ESKD diagnosis/procedure[1] or at least 2 dialysis diagnoses/procedures[1] separated by ≥ 28 days or eGFR<15 on 2 measurements separated by ≥ 28 days *The second eGFR measurement is required to be within 2 years from index, at which time, all patients will be censored (See Section

9.3.2.2 Secondary outcomes

Table 3 Secondary outcomes included in this study

Outcomes	**Definition[1]**
Secondary Renal Effectiveness Outcomes	
Secondary outcome 1: 40% decline in eGFR	Same as that used for the primary composite outcome
Secondary outcome 2: Incident end-stage kidney disease (ESKD)	As for ESRD definition from primary composite outcome
Secondary outcome 3: Dialysis	Incident dialysis, given dialysis in the 12 months preceding index date is a disqualifying diagnosis/procedure
Secondary outcome 4: Kidney transplant	Any procedure[1] associated with healthcare encounters, including hospitalizations and specialist outpatient and primary care encounters
Secondary CV Effectiveness Outcomes	
Secondary outcome 5: Composite outcome including Hospitalization for heart failure All-cause death	Any diagnosis[1] of heart failure associated with hospital admission, including inpatient and ED to inpatient encounters. From death records provided by sites, supplemented with linkage using Datavant Software.

Outcomes	**Definition[1]**
Secondary outcome 6: Hospitalization for heart failure	Any diagnosis[1] associated with hospital admission, including inpatient and emergency department (ED) to inpatient encounters
Secondary outcome 7: All-cause death	From death records provided by sites, supplemented with linkage using Datavant Software.
Secondary outcome 8: Composite outcome including MI[2] Stroke[2] All-cause death Coronary revascularization procedure	For MI and stroke, any inpatient diagnosis[2] associated with healthcare encounters, including inpatient and ED to inpatient For all-cause death, as for secondary outcome 7
Secondary outcome 9: Composite outcome including MI[2] Stroke[2] All-cause death	For MI and stroke, any inpatient diagnosis[2] associated with healthcare encounters, including inpatient and ED to inpatient For all-cause death, as for secondary outcome 7
Secondary safety outcomes	
Secondary outcome 10: Diabetic ketoacidosis	Any diagnosis[1] associated with healthcare encounters in the inpatient setting
Secondary outcome 11: Severe hypoglycemia	Any diagnosis[1] associated with healthcare encounters in the inpatient or ED setting
Secondary outcome 12: Urinary tract cancer	Two or more diagnoses[1] associated with healthcare encounters within 2 months
Secondary outcome 13: Severe Urinary Tract Infections (UTI)	Any diagnosis[1] associated with healthcare encounters in the inpatient or ED setting for: Pyelonephritis (ICD-10 codes in Annex Table 5-6) Urosepsis. Combination of diagnosis code for UTI and a diagnosis code for sepsis within 1 week (ICD-10 codes for sepsis in Annex Table 5-6, ICD-10 codes for UTI in Annex Table 5-8). In order to rule out nosocomial infection, at least one of the following criteria will have

Outcomes	Definition[1]
	to be present within 7 days prior to the hospital admission: Prescription for an antimicrobial agent Outpatient visit with a recorded diagnosis code for UTI or pyelonephritis Outpatient visit with a recorded diagnosis code for UTI or pyelonephritis
Secondary outcome 14: Acute kidney injury that requires dialysis	Any diagnosis[1] associated with inpatient healthcare encounters for AKI plus at least one inpatient encounter indicating dialysis within 28 days of the AKI encounter Two or more dialysis encounters separated by 28 days or more will be excluded from this definition
Secondary outcome 15: Genital Mycotic infection	Any diagnosis associated with healthcare encounters, including hospitalizations and outpatient encounters, or prescription for fluconazole

1 Detailed variable definitions for the outcomes will be defined based on ICD diagnosis and procedure codes and CPT codes;

2 As heart failure, MI and stroke are defined from diagnosis without mortality data, the outcomes include both fatal and non-fatal events.

9.3.3 Covariates

The overall list of covariates being examined in this investigation is provided in the study SEAP. The SEAP provides an overview of the variables that will either be included in the propensity score modeling for patient matching or presented in descriptive analyses for the baseline variables but will not be included in PS modeling.

9.4 DATA SOURCES

This study will utilize high-quality renal function laboratory data available in medical electronic health records from approximately 20 health systems in the US that have mapped their data to the PCORnet CDM. Sites meeting PCORnet data curation quality checks will be eligible to participate in this study. Sites will be approached for participation in this study based on an initial feasibility assessment to determine the extent and completeness of key data elements (renal laboratory data, prescription data, relevant medical diagnoses, and data from both inpatient and outpatient encounters). Death data will be ascertained from site records and augmented with de-identified encrypted linkage to external sources, which includes reported deaths from the government and commercial obituaries using Datavant Software.

9.5 STUDY SIZE

The estimated required sample size for the primary analysis depends on the incidence rate of the primary composite renal outcome in the reference cohort, and the difference in effectiveness of comparison drugs (hazard ratio, HR) (Table 4). Incidence rates ranging from 13 per 1,000 patient years to 46 per 1,000 patient years (DAPA-CKD SGLT2i cohort) [R21-1080] were considered as representative of anticipated incidence rates in the non-DKD and DKD subgroups. Sample size was estimated to achieve 80% power for a two-sided log rank test with type 1 error of 0.05. Calculations assumed 12 months accrual and 12 months additional follow-up, for a median follow-up of 18 months. Assuming an incidence rate of 30 per 1,000 patient years in the overall cohort, a sample size of approximately N=7,600 per group is estimated to have 80% power to detect a hazard ratio of 0.80. For a subgroup with a higher incidence rate (e.g., 46 per 1,000 patient years), similar power could be achieved with an approximate sample size of N=5,000 per group.

Table 4 Sample size per group, as a function of incidence rate of primary renal outcome and hazard ratio

	Hazard Ratio					
Reference Group Incidence Rate*	**0.60**	**0.65**	**0.70**	**0.75**	**0.80**	**0.85**
13	3843	5178	7264	10771	17316	31648
30	1682	2268	3183	4721	7593	13883
46	1108	1494	2097	3112	5007	9158

* Assumed hazard rate (per 1,000 patient years) in reference cohort

9.6 DATA MANAGEMENT

The data will be extracted through standardized SAS queries that are distributed to health systems and executed against the most recently approved PCORnet CDM. Data will be delivered to [redacted] via secure shared Box folders and linked to death data using Datavant Software. All analyses will be performed using SAS v9.4 or R. Only individuals on the IRB for this project will have access to the data, and it will all be stored on secure servers behind the [redacted] firewall.

Missing data (e.g., for demographics, vital signs, lab measures) will be documented to report extent of missingness. Missing data will be excluded from denominators in descriptive summaries. For regression models, extent of missing covariate data will be evaluated and appropriate measures for covariates will be taken. This may include multiple imputation or defining the covariate differently, when possible.

For diagnoses, procedures and medications, absence of a relevant code during the specified time window will be interpreted as ‘no evidence’. For these factors we hope to avoid possible

misclassification through appropriate eligibility criteria (e.g., restricting to patients with evidence of interaction within the health system). For time-to-event analyses, follow-up will be censored early if patient has lost contact with the health system (defined as 18 months after last encounter with the health system).

9.7 DATA ANALYSIS

Below is an overview of the statistical analyses planned for this project and the approach to implementation of the analyses.

9.7.1 Phased Implementation of Analyses

A phased approach to implementation of data analyses will be used to allow examination of key aspects of the patient populations by treatment group and the prescribing practices by treatment type (i.e., empagliflozin, any SGLT2i, DPP4i and (if feasible) GLP1RA). A first phase of the analyses will focus on descriptive evaluation of differences in demographic and clinical patient characteristics, number and timing of prescriptions across treatment groups, and summary of outcome event rates aggregated across treatment arms. The main rationale for this phased analytic approach is to examine the potential for exposure misclassification due to the limited medication exposure data available in PCORnet (e.g., no pharmacy claims data). Secondary goals of the initial phase will be to assess the degree to which patient characteristics have been well balanced after propensity score weighting, and to confirm that the study will have adequate statistical power based on observed sample size and aggregate event rates for key outcomes. Results from this first analytic phase will be examined and discussed by members of the study team (BI and [redacted]) prior to implementation of comparative outcome analysis to provide an opportunity for modification of the study protocol (if needed) and/or study discontinuation if determined appropriate. Additional details for the phased analytic approach, along with codelists and table shells, are provided in the SEAP.

9.7.2 Main analysis

9.7.2.1 Describe the demographic and clinical characteristics of the overall cohort, stratified by DKD status and drug comparator

Analysis: Baseline characteristics will be presented separately for each comparison cohort identified in sections above, resulting in one set of tables for each 2-arm comparison. Characteristics will include demographics, medical history, lab values, and concomitant medications. Continuous variables will be summarized as mean (standard deviation), median [25th percentile, 75th percentile], 5th and 95th percentiles, and minimum, maximum. Categorical variables will be presented as frequencies (%), as will any continuous variable that is further categorized.

Characteristics will be presented in the unweighted cohorts. Additionally, characteristics will be stratified by DKD status and drug comparators. The degree of imbalance in variables

between comparator arms will be quantified with absolute standardized mean differences (see also Objective 2).

9.7.2.2 Generate propensity score models and overlap weights

Analysis: We will use post-LASSO overlap weighting to create the weights for analysis within the DKD and no DKD groups separately. For each two-arm study, propensity score models will be built using a logistic LASSO model with the covariates of interest and all subgroup (see section below) by covariate pairwise interactions. The outcome of interest is treatment group, with empagliflozin [or any SGLT2i] as the treatment group of interest and DPP4i [or GLP1RA] as the reference treatment. In the post-LASSO approach, the variables/interactions that are remaining in the LASSO model are refit to a standard logistic regression to get the final propensity score estimates and weights (effects/probabilities from the LASSO model would have faults due to shrinkage of the coefficient estimates) and the overlap weights. The predicted probabilities from the refit logistic regression are considered the propensity scores. For patients on the reference treatment, the overlap weight is the same as the PS. For patients on the treatment of interest, the overlap weight is 1-PS. No trimming is required due to the PS weights being bounded between 0 and 1.

For each patient, the overlap weight is the predicted propensity that the patient received the treatment opposite from what they were initiated on. For example, for the comparison of empagliflozin versus DPP4i initiation, a patient who was initiated on empagliflozin will receive a weight equal to (1-ps), where ‘ps’ is the estimated propensity score for empagliflozin initiation, and a patient who was initiated on DPP4i is weighted by ‘ps’.

Baseline characteristics will be presented in the reweighted populations. Distributions of covariates in the DKD and no DKD groups and further within subgroups of interest will be assessed using standardized mean differences. Absolute standardized mean differences will be visually depicted using the CONNECT-S plot. Absolute standardized mean differences should be below 0.10 across covariates and subgroups but those that are less than 0.25 might be acceptable.

9.7.2.3 Determine the effect of empagliflozin compared to DPP4i on outcomes

Analysis: The effect of empagliflozin compared to DPP4i on outcomes will be assessed using Cox proportional hazards models in a 2-arm comparison. The analysis will include all patients with a valid overlap weight and will be done for overall and within DKD subgroups. The main analysis will assess outcomes while patients remain on initial treatment.

Follow-up will start the day after the index date (date of initiation of empagliflozin or DPP4i) and will continue until the first occurrence of the outcome of interest, or end of study date (date of death, date of study end, 2 years after index date). For the main AT analysis, follow up will be censored early if an empagliflozin user starts a DPP4i or other type of SGLT2i, or if a DPP4i user starts any SGLT2i. For the AT analysis, if an empagliflozin or DPP4i user initiates a GLP1RA, this will be adjusted for in the model using a time-dependent indicator

variable. Additionally, follow-up will be censored early if there is no indication of a new prescription in the year (+30 days) following the last observed prescription.

Incidence rates will be computed as the number of first events per 100 patient years of follow-up. Analyses of time to first event will be performed using Cox proportional hazards models. Outcomes where death is a competing risk will be analyzed using cause-specific proportional hazards models, achieved by censoring follow-up at the time of death. All analyses will be adjusted for covariates (variables) that continue to be unbalanced after reweighting, with any additional covariates that might be of medical interest identified by the clinicians. Hazard ratios comparing empagliflozin to DPP4i with 95% confidence intervals and the adjusted two-sided p-values for superiority testing will be presented for all outcomes.

Kaplan-Meier curves will be created for each outcome in the overall and DKD subgroups using the reweighted population. Kaplan-Meier curves will also be generated to summarize the cumulative incidence of treatment switching by comparator arm.

9.7.2.4 Determine the effect of SGLT2i compared to GLP1RA on outcomes

Analysis: Repeat objective 3 with the secondary comparison cohort of initiators of any SGLT2i or GLP1RA. In this analysis, follow up will be censored early if a SGLT2i user starts a GLP1RA, or if a GLP1RA user starts any SGLT2i. If a SGLT2i or GLP1RA user initiates a DPP4 inhibitor, this will be adjusted for in the model.

[redacted]

9.8 QUALITY CONTROL

The quality control, review, and monitoring plan are summarized below. Greater details are documented in the study DMRP.

Validation or quality control (QC) refers to establishing by objective evidence that requirements of programming tasks have been implemented correctly and completely. To ensure these requirements are met, internal and beta testing is performed for every query according to applicable standard operating procedures (SOP). Data quality checks will include evaluating variable distributions to identify extreme outliers, which will be handled with input from the [redacted] clinical PI. Key variables will be evaluated for unusual patterns of missingness or distributions over time and by site.

A Study Specific Data Characterization (SSDC) query will also be deployed to the selected sites to confirm data availability, completeness, conformance to the CDM specifications and study feasibility prior to the final production query. The SSDC will provide descriptive statistics of the data that will allow for an early evaluation of variable distributions. These results can often provide insights for local institutions to refine their data, and possibly refresh prior to the final query.

Additionally, as part of general QC standards, SAS log files will be saved after each production run and inspected for errors and warnings after each run by the program author. Log files will be free from ERROR messages, and any WARNINGS or problematic NOTEs, such as those concerning uninitialized variables or multi-record merging, etc., should be investigated and, if allowed to remain, should be reviewed with the lead statistician, with input from the statistical mentor if needed.

The statistical mentor will review new statistical results before they are released to the internal team, or in parallel (if timelines necessitate), and will review programming specifications and/or code as requested by the lead statistician, or as needed based on an assessment of risk. The [redacted] clinical PI will review new statistical results before they are released to the sponsor.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Limitations of the study include:

- Limitations inherent to all EHR-based studies, including potential for missing data (i.e., data that was generated through a different health system) or inaccurate data based on billing codes
- The data will represent 20 large US health systems but may not be representative of or generalizable to the entire US population
- Only the presence of a prescription will be used to identify drug exposure since due to the nature of US EHR data, which includes the unavailability of more detailed treatment exposure data is not available in PCORnet (i.e., no data are available for number of pills, or numbers of refills, days supply, or discontinuation orders). However, to account for the maximal days supply provided in the US, patients). Patients will be censored at 12 months following index prescription (with a 30-day grace period), which allows for the maximal amount of time a single prescription in the US is provided if no subsequent prescriptions are observed. In EMPRISE US [P21-10532], approximately 40% of patients were censored due to treatment discontinuation and the mean follow-up time on treatment was approximately 6 months in both exposure groups. Therefore, patients in However, the current study may be followed beyond time of medication exposure. ability to estimate drug exposure using more accurate approaches commonly implemented in real-world studies using claims data (e.g., calculation of days supply) will not be possible. This limitation could result in higher than actual number of person years of follow-up time beyond actual drug exposure, which could lead to attenuation of the estimated risk differences between treatment groups.
- With the advent of COVID, less laboratory and encounter data may have been collected, though we do not anticipate that this would differ by medication type
- Despite adjusting for numerous factors, there may be unmeasured confounders that impact the estimated differences in risk across treatment groups in this analysis
- eGFR data may not have been obtained as a part of routine clinical care, or the laboratory data may be missing, which is a potential limitation in all EHR analyses.

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.

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, Guidelines for Good Pharmacoepidemiology Practice (GPP), and the relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains 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.

10.1 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The study design involves only the analysis of retrospective data that was collected from the patient records in an aggregate manner. However, if during the study conduct, [redacted] incidentally uncovers an adverse event (AE) associated with the use of Empagliflozin or any BI product, that will be reported according to local regulatory requirements for spontaneous AE reporting.

10.2 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This NIS 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.

10.3 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.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

We will plan to submit both an abstract to a major CV scientific congress, as well as a manuscript to a leading CV peer-reviewed journal. We will also disseminate results to the public using methods endorsed by our stakeholder advisory group.

The rights of the investigator and of the sponsor regarding 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.

12. REFERENCES

12.1 PUBLISHED REFERENCES

Reference	BI Document Number
Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, de Boer IH. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol, 2013. (PMID: 23362314)	R13-0685
Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clin J Am Soc Nephrol, 2017. (PMID: 28522654)	P18-00615
Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, Malanda B. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract, 2018 (PMID: 29496507)	R21-4492
Fleurence RL, Curtis LH, Califf RM, Platt R, Selby JV, Brown JS. Launching PCORnet, a national patient-centered clinical research network. J Am Med Inform Assoc, 2014. (PMID: 24821743)	R21-4494
Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde AM, Wheeler DC; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med, (PMID: 32970396)	R21-1080
Levin A, Agarwal R, Herrington WG, Heerspink HL, Mann JFE, Shahinfar S, Tuttle KR, Donner JA, Jha V, Nangaku M, de Zeeuw D, Jardine MJ, Mahaffey KW, Thompson AM, Beaucage M, Chong K, Roberts GV, Sunwold D, Vorster H, Warren M, Damster S, Malik C, Perkovic V; participant authors of the International Society of Nephrology's 1st International Consensus Meeting on Defining Kidney Failure in Clinical Trials. International consensus definitions of clinical trial outcomes for kidney failure: 2020. Kidney Int., 2020. (PMID: 32998816.)	R21-4243
Li F, Morgan KL, and Zaslavsky AM. Balancing covariates via propensity score weighting. J Am Statistical Assoc, 2018.	R20-1964
Mann JFE, Ørsted DD, Brown-Frandsen K, Marso SP, Poulter NR, Rasmussen S, Tornøe K, Zinman B, Buse JB; LEADER Steering Committee and Investigators. Liraglutide and Renal Outcomes in Type 2 Diabetes. N Engl J Med, 2017. (PMID: 28854085)	R21-4493

Reference	BI Document Number
Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med, 2016. PMID (27295427)	R17-1732
Packer M. Worsening Heart Failure During the Use of DPP-4 Inhibitors: Pathophysiological Mechanisms, Clinical Risks, and Potential Influence of Concomitant Antidiabetic Medications. JACC Heart Fail, 2018. (PMID: 29525332)	R18-1139
Patorno E, Pawar A, Wexler DJ, Glynn RJ, Bessette LG, Paik JM, Najafzadeh M, Brodovicz KG, Déruaz-Luyet A, Schneeweiss S. Effectiveness and safety of empagliflozin in routine care patients: Results from the EMPagliflozin compaRative effectIveness and SafEty (EMPRISE) study. Diabetes Obes Metab, 2022. (PMID: 34729891)	P21-10532
Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med, 2019. (PMID: 30990260)	R19-1356
Thomas LE, Li F, Pencina MJ. 2020. Overlap weighting: a propensity score method that mimics attributes of a randomized clinical trial. JAMA, 2020. (PMID: 32369102)	R21-4495
Tohidi M, Hasheminia M, Mohebi R, et al. Incidence of chronic kidney disease and its risk factors, results of over 10 year follow up in an Iranian cohort. PLoSOne 201;7(9):e45304. (PMID: 23028919)	R21-4496
USRDS: United States Renal Data System Annual Data Report: Epidemiology of Kidney Disease in the United States, Bethesda, MD, National Institute of Diabetes and Digestive and Kidney Diseases, 2015.	R19-1661
Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC, Zinman B; EMPA-REG OUTCOME Investigators. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med, 2016. (PMID: 27299675)	P16-06807
Yang S, Lorenzi E, Papadogeorgou G, Wojdyla DM, Li F, Thomas LE. Propensity score weighting for causal subgroup analysis. Stat Med.	R21-4497

Reference	BI Document Number
2021. (PMID: 33982316)	
Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med, 2015. (PMID: 26378978)	P15-09840

12.2 UNPUBLISHED REFERENCES

Not applicable

13. ANNEXURES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Description	Date	Title
1	c39368586-01	Study Protocol (V 1.0)	30 June 2022	Comparative cardiovascular and renal effectiveness and safety of Empagliflozin and other SGLT2i in patients with type 2 diabetes (T2D) with and without baseline kidney disease in the United States
2	c39712001-01	Statistical and Epidemiological Analysis Plan (V 1.0)	8 July 2022	Statistical and Epidemiological Analysis Plan (SEAP) for Non-Interventional Study (NIS) to compare cardiovascular and renal effectiveness and safety of Empagliflozin and other SGLT2i in patients with type 2 diabetes (T2D) with and without baseline kidney disease in the United States – Version 1.0

Number	Document reference number	Description	Date	Title
3	c39712001-02	Statistical and Epidemiological Analysis Plan (V 2.0)	TBD	Statistical and Epidemiological Analysis Plan (SEAP) for Non-Interventional Study (NIS) to compare cardiovascular and renal effectiveness and safety of Empagliflozin and other SGLT2i in patients with type 2 diabetes (T2D) with and without baseline kidney disease in the United States – Version 2.0
4	NA	Data Management and Review Plan	18 July 2022	Comparative cardiovascular and renal effectiveness and safety of Empagliflozin and other SGLT2i in patients with type 2 diabetes (T2D) with and without baseline kidney disease in the United States: Data Management and Review Plan
5	c39712001-02	Study codelist (included with SEAP)	15June2023	*1245.0228 Empa DKD Codelist Master with Sources 15June2023*

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	NA
1.1.4 Interim report(s)	☐	☐	☒	NA
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	NA
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	NA

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10.1

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2.3
4.2.2 Age and sex	☒	☐	☐	9.2.2
4.2.3 Country of origin	☒	☐	☐	9.2.1

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.4 Disease/indication	☒	☐	☐	9.2.2
4.2.5 Duration of follow-up	☒	☐	☐	9.2.3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	--
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.2.3
5.4 Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	NA
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.3.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2.1-2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2.1-2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	--

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	NA

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7.1
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.2.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☒	☐	--

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4, SEAP
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4, SEAP
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4, SEAP
9.2 Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	SEAP
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.3, SEAP
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3, SEAP
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1, SEAP
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2.1-2, SEAP
9.3.3 Covariates and other characteristics?	☒	☐	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4, SEAP

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.1
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.8
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	--
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.6
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.2

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8, 9.10
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	--

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	SEAP
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.1, 9.2.1, 9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	NA
13.3 Have data protection requirements been described?	☒	☐	☐	9.6

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☐	☐	☒	NA
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Name of the main author of the protocol: [redacted]

Date: 3/May/2022

Main Author Signature: _____

ANNEX 3. REVIEWERS AND APPROVAL SIGNATURES

PRINCIPAL INVESTIGATOR SIGNATURE

Study Title: Comparative cardiovascular and renal effectiveness and safety of Empagliflozin and other SGLT2i in patients with type 2 diabetes (T2D) with and without baseline kidney disease in the United States

Trial Number: 1245-0228

Study Protocol version: 2.0

I herewith certify that I agree to content of the Study Protocol 2.0 and to all documents referenced in the Study Protocol version 2.0.

Date: **14 July 2023**

Name: [redacted]

Signature: DocuSigned by: [redacted] 14-Jul-2023
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 14-Jul-2023 | 6:31:59 AM PDT
[redacted]

Affiliation: [redacted]

APPROVAL / SIGNATURE PAGE

Document Number: c39368586 **Technical Version Number:2.0**

Document Name: bi-dkd-protocol-v1.4-10jun2022

Title: Comparative cardiovascular and renal effectiveness and safety of Empagliflozin and other SGLT2i in patients with type 2 diabetes (T2D) with and without baseline kidney disease in the United States

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval	[redacted]	31 Jul 2023 08:13 CEST
Approval-Clinical Trial Leader		08 Aug 2023 14:33 CEST
Approval-On behalf of [redacted] or [redacted] or [redacted]		09 Aug 2023 15:43 CEST
Approval-Clinical Program [redacted]		10 Aug 2023 15:35 CEST
Approval		14 Aug 2023 19:26 CEST
Approval		17 Aug 2023 16:53 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed