Non-Interventional Study (NIS) Protocol *Template*

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(1) Note that Instructional text is in red italics,
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(3) Do not change the structure of the template,
(4) Replace all sections in red angle brackets <…>with the appropriate project-specific content,
(5) Don't use red as text color.

This template complies with the current European Medicines Agency requirements on format, layout and content of a Post Authorization Safety Study (PASS) protocol. This protocol template is to be used for all non-interventional studies.

Document Number:	***<Document number from Document Management System (DMS) for submission documents, if relevant>***
BI Study Number:	*<Study Number from CTMS>*
BI Investigational Product(s):	Empagliflozin
Title:	Clinical and economic impact of 2nd line initiation of empagliflozin after metformin, as compared to 2nd line initiation of sulfonylurea after metformin in patients with type 2 diabetes and cardiovascular disease
Brief lay title:	Clinical outcomes and HCRUs in patients with type 2 diabetes and cardiovascular disease on 2nd line empagliflozin versus 2nd line sulfonylureas
Protocol version identifier:	*<Number>*
Date of last version of protocol:	*<Date>*
PASS:	*Insert <Yes> or <No>*
EU PAS register number:	*If applicable, insert <Registration number in the EU PAS register; indicate "Study not registered" if the study has not been registered in the EU PAS register>*
Active substance:	*<List of pharmacotherapeutic group(s) (ACT codes) and active substance(s) subject to the study, if applicable>*
Medicinal product:	*<List of centrally authorised medicinal product(s) and/or, if possible, of nationally authorised products subject to the study, if applicable>*

Product reference:	*<Reference number(s) of centrally authorised products and/or, if possible, of nationally authorised products subject to the study, if applicable>*
Procedure number:	*If applicable, <Agency or national procedure number(s), e.g. EMA/X/X/XXX>*
Marketing authorisation holder(s):	*<Marketing authorisation holder(s) which initiate(s), manage(s) or finance(s) the study>*
Joint PASS:	*If applicable, insert <Yes> or <No>*
Research question and objectives:	Evaluate clinical outcomes (specifically cardiovascular outcomes like hospitalization for heart failure), and healthcare cost and resource utilization, among patients on empagliflozin as monotherapy or as an add-on therapy to metformin versus patients on sulfonylureas as an add-on therapy to metformin, in patients with T2D and CVD.
Country(-ies) of study:	United States
Author:	Effie Kuti, Effie.Kuti@boehringer-ingelheim.com and Christina Cool, Christina.Cool@PrecisionVH.com
Marketing authorisation holder(s):	*<Name, address and contact details of the marketing authorisation holder(s)>*
In case of PASS, add: **MAH contact person:**	*In case of PASS, insert <Name of contact person for this PASS protocol submission (if this a joint PASS, only one person should be mentioned)>*
In case of PASS, add: **<EU-QPPV:>**	*In case of PASS, insert <Name and contact details of the EU-QPPV or his/her delegate>*
In case of PASS, add: **<Signature of EU-QPPV:>**	*In case of PASS, insert <The signature of the EU-QPPV is provided electronically>*
Date:	6/1/2021
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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
CA	Competent Authority
CCDS	Company Core Data Sheet
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
CVD	Cardiovascular Disease
eCRF	Electronic Case Report Form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
HCRU	Healthcare Cost and Resource Utilization
HHF	Hospitalization from Heart Failure
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
PASS	Post-Authorization Safety Study
SAE	Serious Adverse Event
T2D	Type 2 Diabetes

Adapt and complete as appropriate

3. RESPONSIBLE PARTIES

<List of all main responsible parties including the BI NIS lead, the principal investigator, a coordinating investigator for each country in which the study is to be performed (if applies), study site(s)/data source(s) and other relevant study sites must be listed. Contact details and the list of all investigators can be kept in a stand-alone document to be listed in Annex 1 and to be available upon request.

In case of a Joint PASS, any sharing of responsibilities (e.g. for management of adverse events) or distribution of tasks between marketing authorisation holders and other responsible parties must be mentioned in this section. Contact persons for each marketing authorisation holder must be mentioned.>

4. ABSTRACT

The abstract will be disclosed per the NIS SOP, if applicable, so must provide the appropriate level of detail.

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: *If applicable, list <Centrally-authorised medicinal product(s) subject to the study.>*			
Name of active ingredient: *List <Pharmacotherapeutic group(s){ACT codes} and active substance(s) subject to the study>*			
Protocol date: *1 June 2021*	**Study number:**	**Version/Revision:**	**Version/Revision date:**
Title of study:	Clinical and economic impact of 2nd line initiation of empagliflozin after metformin, as compared to 2nd line initiation of sulfonylurea after metformin in patients with type 2 diabetes and cardiovascular disease.		
Rationale and background:	There are no studies comparing the real-world clinical and economic outcomes of patients prescribed empagliflozin as an add-on therapy to metformin versus patients prescribed sulfonylureas as an add-on therapy to metformin. Given the known benefits of empagliflozin in the T2D population and among those with underlying CVD, understanding the current patterns of care and outcomes is important to establish the potential value of increasing use and earlier access to empagliflozin in this high-risk population.		

Research question and objectives:	*Provide a clear statement of the objective(s) of the study, i.e. describe what the study aims to investigate; ideally, should not exceed 3 sentences.* We will evaluate clinical outcomes (specifically cardiovascular outcomes like hospitalization for heart failure), and healthcare cost, and resource utilization, among patients on empagliflozin as an add-on therapy to metformin versus patients on sulfonylureas as an add-on therapy to metformin in patients with T2D and CVD. Our primary objective is to compare incidence of HHF between the two aforementioned patient populations. The secondary outcomes are comparison of all-cause HCRU outcomes: hospitalizations, emergency department (ED) visits, length of stay, number of filled drugs, outpatient visits and all-cause costs: total cost of care, divided by medical (inpatient costs, outpatient costs, emergency costs) and pharmacy costs (all reported in Per Patient Per Month (PPPM) costs) As exploratory analysis 2 point MACE, a composite outcome of myocardial infarction (MI), stroke, or coronary revascularization. *For disclosure purposes: Brief Summary (Purpose): Short description of the protocol intended for the lay public. Include a brief statement of the study hypothesis. (Limit: 5000 characters)* Given the known benefits of empagliflozin in the T2D population and among those with underlying CVD, understanding the current patterns of care and outcomes is important to establish the potential value of increasing use and earlier access to empagliflozin in this high-risk population. This protocol outlines a non-interventional study using existing data that will compare the clinical and economic outcomes among patients on empagliflozin as an add-on therapy to metformin versus patients on sulfonylureas as an add-on therapy to metformin, in patients with T2D and CVD. This study will utilize IQVIA's Real-World Data (RWD) Adjudicated Claims Database (formerly known as PharMetrics Plus) to construct its analytic dataset. Propensity-score matching will be applied to minimize risk of confounding relationships in the dataset that result from any differences between patients of the two different prescribed medications.
Study design:	This study will be a non-interventional study using existing data from January 1, 2014 to the date of the latest available data from IQVIA (detailed below). Data available after March 31, 2020 will not be used due to the potential confounding events of coronavirus. The study will analyze the clinical and economic effect of empagliflozin in T2D patients with CVD. Empagliflozin initiators as an add-on therapy to metformin, comprise the treatment population. Patients initiating sulfonylureas as add-on to metformin comprise the control population.

Population:	IQVIA's claims database is composed of more than 190 million unique enrollees from national and sub-national health plans and self-insured employer groups from 2006 to the present. The database is considered representative of the gender and age demographics of the insured United States population. Inclusion criteria: • Prevalent metformin use + initiation of empagliflozin OR prevalent metformin use + initiation of a sulfonylurea • ≥18 years of age at index date during study observation • ≥1 inpatient and/or ≥ 2 outpatient claims denoting T2D diagnosis (in any position) in the 12 months prior to index date (Diagnosis codes available in the appendix **Error! Reference source not found.**) • ≥1 inpatient and/or ≥2 outpatient claims denoting CVD (in any position) diagnosis in the 12 months prior to index date (Diagnosis codes available in the additional workbooks "ICD 9 Dx Codes.xlsx" and "ICD 10 Dx Codes.xlsx") • ≥12 months of no exposure to T2D medications in the pre-index period (excluding metformin in both arms) • ≥2 months post-index date • ≥12 months of continuous enrollment prior to index date Exclusion criteria: • Diagnosis of Type 1 Diabetes, secondary, or gestational diabetes in the 12 months prior to index date (Diagnosis codes available in the additional workbooks "ICD 9 Dx Codes.xlsx" and "ICD 10 Dx Codes.xlsx")) • Diagnosis of severe comorbidities including malignancy, end-stage renal disease, human immunodeficiency virus, Hepatitis C infection, or organ transplant in the 12 months prior to index date (Diagnosis codes available in the additional workbooks "ICD 9 Dx Codes.xlsx" and "ICD 10 Dx Codes.xlsx") • Admission to nursing home in the 12 months prior to index date

Variables:	Exposure: ▪ Treatment with Empagliflozin as add-on to metformin versus Treatment with Sulfonylurea as add-on to metformin Baseline Characteristics (Covariates): ▪ Demographics o E.g. Age, sex, geographic identifier, and time-of-entry indicator ▪ Calendar time of cohort entry (in quarters and days) ▪ Comorbidities/previous health events o E.g. Ischemic heart disease, hypertension, hyperlipidemia, chronic kidney disease, ischaemic or haemorrhagic stroke, peripheral arterial disease or surgery, oedema ▪ Diabetes-related complications, o E.g. Diabetic neuropathy, diabetic retinopathy, hospitalized hypoglycemia ▪ Use of diabetes drugs o Length of metformin use ▪ Use of other medications o E.g. Angiotensin converting enzyme inhibitors, Beta-blockers, calcium-channel blockers ▪ Lifestyle factors o E.g. Obesity, Overweight, smoker ▪ Previous healthcare utilization o E.g. Previous coronary revascularization, Endocrinologist visit within prior 30 days, Cardiologist visit within prior 30 days, etc. Outcomes: Primary outcome ▪ First hospitalization for congestive heart failure (HHF) (we will first analyze this by looking at diagnosis code in any position, we will then run the analysis considering diagnosis coding in either the principal or secondary position). Secondary outcomes ▪ Healthcare utilization outcomes: hospitalizations, emergency department (ED) visits, length of stay, number of filled drugs, outpatient visits

	▪ All cause cost outcomes: Total cost of care, divided by medical (inpatient costs, outpatient costs, emergency costs) and pharmacy costs (all reported in Per Patient Per Month (PPPM) costs) Exploratory outcome ▪ Effectiveness outcomes: 2 point MACE as a Composite Score of myocardial infarction, stroke, or coronary revascularization
Data sources:	IQVIA's Real-World Data (RWD) Adjudicated Claims Database (formerly known as PharMetrics Plus)
Study size:	See Study Size section below for detailed descripted of power calculations. Our estimation corresponds to a minimum and maximum number of events (HHF in both cohorts) required for a powered analysis of 169 and 470 total HHF events between both cohorts.
Data analysis:	Propensity scores will be calculated using the listed covariates (below) and used to construct PSM cohorts, if the post-matching sample size still allows for a powered analysis, or IPTW cohorts if not. Using observed clinical events, we will calculate incidence rates and 95% confidence intervals for PSM (or IPTW) cohorts. We will estimate the hazard ratios and confidence intervals via Cox regression for our primary outcome (HHF). We will also estimate differences in healthcare utilization using incident counts, by performing either Poisson or negative binomial regression. Differences in cost outcomes will be assessed by generalized linear regression using a Gamma family link function. We will also explore instrumental variables that are employed to minimize residual confounding after PSM (or IPTW).
Milestones:	*The database for this analysis will be constructed by March 08, 2021, Data analyses will be complete April 12, 20201. A report of the findings from this study will be complete for review June 7, 2021.*

5. AMENDMENTS AND UPDATES

Write <None> or indicate any substantial amendment and update to the study protocol after the start of data collection in a table as indicated below.

Number	Date	Section of study protocol	Amendment or update	Reason
1	*<DD Month YYYY>*	*<Text>*	*<Text>*	*<Text>*
2	*<DD Month YYYY>*	*<Text>*	*<Text>*	*<Text>*
<n>	*<DD Month YYYY>*	*<Text>*	*<Text>*	*<Text>*

6. MILESTONES

Milestone	Planned Date
Execute 3rd party data agreement	09/15/2020
Precision obtain data for analyses	10/01/2020
Finalize analysis plan	06/07/2021
Construct analytic dataset	07/02/2021
Complete all analyses	07/23/2021
Complete study report	08/27/2021

7. RATIONALE AND BACKGROUND

Approximately 13% of adults in the United States have been diagnosed with diabetes, with approximately 90% of those cases attributable to T2D.[1] Patients with diabetes are at much higher risk for CVD than patients without diabetes, and adults with T2D have a 2-to-4 fold higher risk of cardiovascular morbidity and mortality.[2] The American Heart Association lists T2D as one of the seven major controllable risk factors for CVD, with glycemic control being a contributing factor to cardiac impairments among patients with T2D.[2]

Empagliflozin (Jardiance), is a SGLT2i; this therapy was first approved in 2014 for the reduction of HbA1c in patients with T2D, and is available both as monotherapy and as add-on therapy. In 2016 empagliflozin received a new indication for reducing cardiovascular death in patients with T2D and CVD, and a 2020 update to the American Diabetes Association Standards of Care recommends the addition of either SGLT2i or GLP1-RA for patients with pre-existing cardiovascular disease or kidney disease.[3] In clinical studies, the rate of death in patients taking empagliflozin vs. placebo has been significantly reduced (3.7%, vs. 5.9%; 38% relative risk reduction; p-value <0.001), as have rates of hospitalization for heart failure (HHF) (2.7% vs. 4.1%; 35% relative risk reduction) and all-cause death (5.7% vs. 8.3%; 32% relative risk reduction; p-value 0.002).[4] A 2017 real world claims analysis which studied HHF rates of T2D patients starting canagliflozin, dapagliflozin, or empagliflozin (53%, 42%, and 5% of patients, respectively) found a 39% risk reduction in HHF and 51% risk reduction in all-cause death versus other glucose reducing drugs.[5] The overall safety profile of empagliflozin was found to be similar to that of placebo in the EMPA-REG OUTCOME trial.[6]

Though there are few studies on the cost effectiveness of empagliflozin, current literature suggests it is cost effective versus other antihyperglycemic agents (AHA). Real world analysis of the economic impacts of empagliflozin for patients with T2D demonstrates a per member per month (PMPM) reduction in all-cause healthcare costs of $412 compared to other branded anti-hyperglycemic agents (DPP4-inhibitors, GLP1-agonists, other SGLT2-inhibitors, and

insulins).[7] These costs differences were largely due to lower all-cause medical costs, with there being only a small ($31) cost difference between empagliflozin and other AHA pharmacy costs.[7] This is significant, as the economic cost of diabetes in the United States was estimated at $237 billion in annual direct costs in 2017, and patients with diabetes have medical expenditures over twice as high as those without diabetes.[8,9]

Sulfonylureas are a class of antidiabetic medications which work by stimulating insulin release from pancreatic cells, and include the generics chlorpopamide, glyburide, tolazamide, and tolbutamide.[10] There is some evidence suggesting that sulfonylureas are associated with increased risk of cardiovascular events and mortality. In a review of observational studies comparing metformin and sulfonylureas, the relative risk of adverse events was 13% higher in sulfonylureas patients with a ratio of relative risks of 1.13 (95% CI 1.01-1.27), and the relative risk of death was increased by 20% (RRR 1.20, 95% CI 1.07-1.34).[11] Of note, a review of the cardiovascular profile of diabetic drugs found multiple studies suggesting a detrimental effect on cardiovascular health in patients treated with sulfonylureas.[12] Direct comparisons of sulfonylureas to empagliflozin are currently not available, but evidence suggests that empagliflozin is well tolerated as add on therapy to patients using metformin plus sulfonylureas.[13] Comparisons between the cost effectiveness of sulfonylureas and empagliflozin are not currently available, though previous evidence suggests that metformin is more cost effective than sulfonylureas, with one study estimating an increase of $2,800 over 25 years when glyburdide was used as first line therapy over metformin, while at the same time accumulating 0.17 fewer quality adjusted life year (QALYs).[14]

Given the known benefits of empagliflozin in the T2D population and among those with underlying cardiovascular disease, understanding the current patterns of care and outcomes is important to establish the potential value of increasing use and earlier access to empagliflozin in this high-risk population.

This study would also be the first to assess empagliflozin as second-line after metformin versus second-line initiation of sulfonylureas in the United States using the IQVIA commercial claims database to look at clinical and economic outcomes.

8. RESEARCH QUESTION AND OBJECTIVES

Evaluate clinical outcomes (specifically cardiovascular outcomes like hospitalization for heart failure), and healthcare cost, and resource utilization, among patients on empagliflozin as an add-on therapy to metformin versus patients on sulfonylureas as an add-on therapy to metformin, in patients with T2D and CVD.

Specifically our objectives are the following

1. *Primary Objective*
    a. Compare incidence of HHF between the two aforementioned patient populations.
2. *Secondary Economic Objectives*
    a. Comparisons of HCRU outcomes: hospitalizations, emergency department (ED) visits, length of stay, number of filled drugs, outpatient visits
    b. Comparisons of all-cause cost outcomes: Total cost of care, divided by medical (inpatient costs, outpatient costs, emergency costs) and pharmacy costs (all reported in Per Patient Per Month (PPPM) costs)
3. Exploratory Objective
    a. Comparisons of 2-Point MACE as a Composite Score of myocardial infarcton, stroke or coronary revascularization

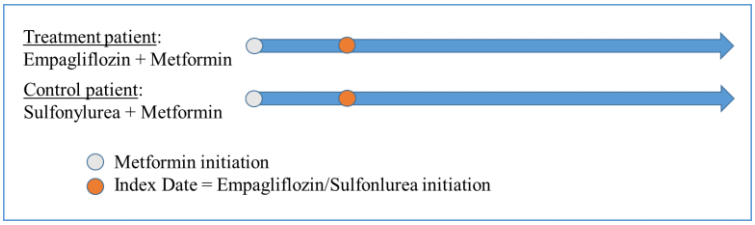
9. RESEARCH METHODS

9.1 STUDY DESIGN

This study will be a non-interventional study using existing data from January 1, 2014 to the date of the latest available data from an IQVIA (detailed below) database. Data available after March 31, 2020 will not be used due to the potential confounding events of coronavirus.

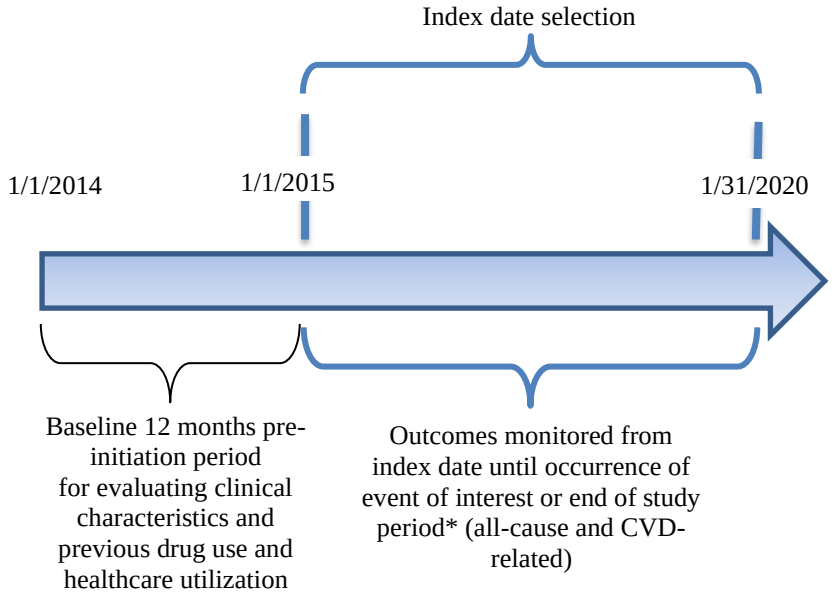
The study will analyze the clinical and economic effect of empagliflozin in Type 2 Diabetes (T2D) patients with Cardiovascular Disease (CVD). Empagliflozin initiators, as an add-on to metformin therapy comprise the treatment population. Patients initiating sulfonylureas as an add-on to metformin comprise the control population.

The index date for the empagliflozin add-on therapy arm is defined as the date of initiation of empagliflozin.



The index date for the sulfonylurea add-on therapy control arm in a format parallel to the definition for the empagliflozin add-on therapy treatment arm, i.e., the index date is defined as the date of initiation of sulfonylurea therapy. We will control for exposure time in our propensity score calculations.

Baseline characteristics for all patients as well as their enrollment status will be confirmed using 12 months of claims data prior to the index date. Cardiovascular events, healthcare utilization, and its associated costs will be observed from the index date until the end of the study period. Outcomes and the associated costs will be monitored and then compared between cases and controls using inverse probability treatment weighting (IPTW), or, as sample size allows, propensity score matching.



*Monitoring period can also be ended by one of the events described in the data analysis section below

For this study, index date selection period will be from 01/01/2015 to 1/31/2020. Follow-up up period for patients not meeting any of the stopping criteria mentioned below will extend until 3/31/2020.

Finally, starting with the initiation of treatment, we observe patient outcomes until one of the following stopping criteria occur:

- discontinuation (defined as a gap in sulfonylurea, empagliflozin, or metformin of >30 days between fills) or switch or addition of a drug in the comparator and/or other antihyperglycemic agents class
- occurrence(s) of an outcome of interest
- nursing home admission
- healthcare plan disenrollment
- end of the study period

9.2 SETTING

N/A

9.2.1 Study sites

N/A

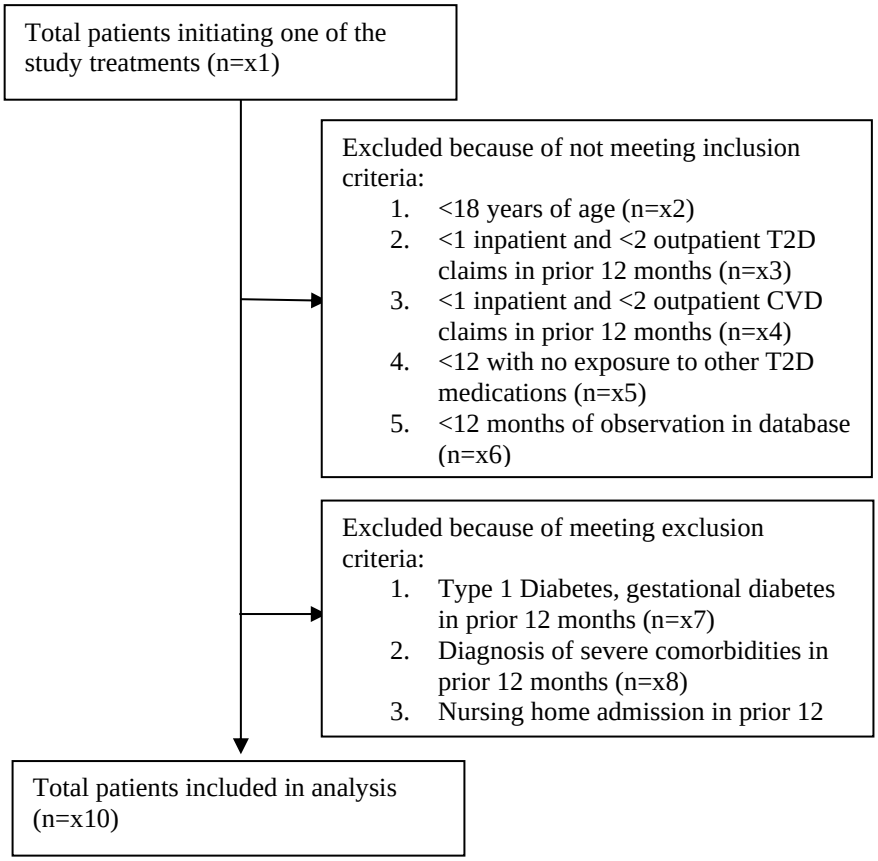
9.2.2 Study population

Inclusion criteria:

- Prevalent metformin use + initiation of empagliflozin OR prevalent metformin use + initiation of a sulfonylurea
- ≥18 years of age at index date during study observation
- ≥1 inpatient and/or ≥ 2 outpatient claims denoting T2D diagnosis (in any position) in the 12 months prior to index date (Diagnosis codes available in the appendix **Error! Reference source not found.**)
- ≥1 inpatient and/or ≥2 outpatient claims denoting CVD (in any position) diagnosis in the 12 months prior to index date (Diagnosis codes available in the additional workbooks "ICD 9 Dx Codes.xlsx" and "ICD 10 Dx Codes.xlsx")
- ≥2 months post-index date
- ≥12 months of no exposure to T2D medications in the pre-index period (excluding metformin in both arms)
- ≥12 months of continuous enrollment prior to index date

Exclusion criteria:

- Diagnosis of Type 1 Diabetes, secondary, or gestational diabetes in the 12 months prior to index date (Diagnosis codes available in the additional workbooks "ICD 9 Dx Codes.xlsx" and "ICD 10 Dx Codes.xlsx"))
- Diagnosis of severe comorbidities including malignancy, end-stage renal disease, human immunodeficiency virus, Hepatitis C infection, or organ transplant in the 12 months prior to index date (Diagnosis codes available in the additional workbooks "ICD 9 Dx Codes.xlsx" and "ICD 10 Dx Codes.xlsx")
- Admission to nursing home in the 12 months prior to index date



9.2.3 Study visits

N/A

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. 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

Exposure cohorts

- Treatment with empagliflozin (as add-on therapy with metformin)
- Treatment with a sulfonylurea (as add-on therapy with metformin)

Exposure will be identified by recorded prescription filling matching the NDC codes for empagliflozin or sulfonylurea, respectively. See list of identifying NDC codes in the additional workbook titled “NDC Codes.xlsx”.

Covariates
Covariates included will be those previously published in the literature.

Baseline characteristics	**Metformin + Sulfonylureas (N =)**	**Metformin + Empagliflozin (N =)**	***St. Diff.***
Age; mean (sd)			
Age categories			
18 - 54; n (%)			
55 - 64; n (%)			
65 - 74; n (%)			
>= 75; n (%)			
Male; n (%)			
Race			
White; n (%)			
Black; n (%)			
Asian; n (%)			
Hispanic; n (%)			
North American Native; n (%)			
Other/Unknown; n (%)			
Region			
Northeast; n (%)			
South; n (%)			
Midwest; n (%)			
West; n (%)			
Quarter and year of cohort entry			
Q3 2014; n (%)			
Q4 2014; n (%)			
Q1 2015; n (%)			
Q2 2015; n (%)			
Q3 2015; n (%)			
Combined comorbidity score; mean (sd)			
No. distinct diagnoses; mean (sd)			
Diabetic nephropathy; n (%)			
Diabetic retinopathy; n (%)			
Diabetes with other ophthalmic conditions or ophtalmic procedures; n (%)			
Diabetic neuropathy; n (%)			
Diabetes with peripheral circulatory disorders; n (%)			

Diabetic Foot; n (%)			
Lower extremity amputation; n (%)			
Skin infections; n (%)			
Foot ulcer; n (%)			
Erectile dysfunction; n (%)			
Hypoglycemia ; n (%)			
Hyperglycemia; n (%)			
Disorders of fluid electrolyte and acid-base balance; n (%)			
Diabetic ketoacidosis; n (%)			
Hyperosmolar hyperglycemic nonketotic syndrome; n (%)			
Diabetes with unspecified complication; n (%)			
Naive new user; n (%)			
Monotherapy; n (%)			
Dual therapy with metformin; n (%)			
Concomitant initiation or current use of metformin; n (%)			
Concomitant initiation or current use of sulfonylureas; n (%)			
Past use of metformin; n (%)			
Past use of sulfonylureas; n (%)			
Past use of insulin; n (%)			
Past use of GLP-1 RAs; n (%)			
Past use of glitazones; n (%)			
Any use of meglitinides; n (%)			
Any use of alpha-glucosidase inhibitors; n (%)			
Lifestyle factors			
Obesity; n (%)			
Overweight; n (%)			
Smoking; n (%)			
Alcohol abuse or dependence; n (%)			
Drug abuse or dependence; n (%)			
Ischemic heart disease; n (%)			
Acute myocardial infarction; n (%)			
Old myocardial infarction; n (%)			
Unstable angina; n (%)			
Stable angina; n (%)			
Other chronic ischemic heart disease; n (%)			
Previous coronary revascularization; n (%)			
Ischemic or hemorrhagic stroke; n (%)			
Ischemic stroke; n (%)			
Transient ischemic attack; n (%)			

Hemorrhagic stroke and other cerebrovascular disease; n (%)			
Late effects of cerebrovascular disease or procedure; n (%)			
Heart failure; n (%)			
Peripheral arterial disease or surgery; n (%)			
Atrial fibrillation; n (%)			
Other cardiac dysrhythmia; n (%)			
Other cardiovascular disease; n (%)			
Hypertension; n (%)			
Hyperlipidemia ; n (%)			
Edema; n (%)			
Non-diabetic renal dysfunction; n (%)			
Acute kidney injury; n (%)			
Chronic kidney disease; n (%)			
Chronic kidney disease stage 1-2; n (%)			
Chronic kidney disease stage 3+ or dialysis; n (%)			
Hypertensive nephropathy; n (%)			
Miscellaneous renal insufficiency ; n (%)			
Kidney or bladder stones; n (%)			
Urinary tract infections; n (%)			
COPD; n (%)			
Asthma; n (%)			
Obstructive sleep apnea; n (%)			
Pneumonia; n (%)			
Liver disease; n (%)			
Osteoarthritis; n (%)			
Other arthritis, arthropathies and musculoskeletal pain; n (%)			
Dorsopathies; n (%)			
Fractures; n (%)			
Falls; n (%)			
Osteoporosis; n (%)			
Disorders of thyroid gland; n (%)			
Depression; n (%)			
Anxiety; n (%)			
Sleep disorders; n (%)			
Dementia; n (%)			
Delirium; n (%)			
Psychosis; n (%)			
Angiotensin converting enzyme inhibitors; n (%)			
Angiotensin II receptor blockers; n (%)			

Beta-blockers; n (%)			
Calcium-channel blockers; n (%)			
Thiazide diuretics; n (%)			
Loop diuretics; n (%)			
Other diuretics; n (%)			
Nitrates; n (%)			
Other hypertension drugs; n (%)			
Digoxin; n (%)			
Anti-arrhythmics; n (%)			
COPD or asthma medications; n (%)			
Statins; n (%)			
Other lipid-lowering drugs; n (%)			
Antiplatelet agents; n (%)			
Oral anticoagulants; n (%)			
Heparin and other low-molecular weight heparins; n (%)			
Nonsteroidal anti-inflammatory drugs; n (%)			
Oral corticosteroids; n (%)			
Bisphosphonates; n (%)			
Opioids; n (%)			
Antidepressants; n (%)			
Antipsychotics; n (%)			
Anticonvulsants; n (%)			
Benzodiazepines; n (%)			
Other anxiolytics or hypnotics; n (%)			
Dementia medications; n (%)			
Antiparkinsonian medications; n (%)			
Hospitalization within prior 30 days; n (%)			
Hospitalization during prior 31-365 days; n (%)			
No. hospitalizations; mean (sd)			
No. hospital days; mean (sd)			
No. emergency department visits; mean (sd)			
No. office visits; mean (sd)			
Endocrinologist visit within prior 30 days; n (%)			
Endocrinologist visit during prior 31-365 days; n (%)			
No. endocrinologist visits; mean (sd)			
Internal medicine visit within prior 30 days; n (%)			
Internal medicine visit during prior 31-365 days; n (%)			
No. internal medicine visits; mean (sd)			
Cardiologist visit within prior 30 days; n (%)			
Cardiologist visit during prior 31-365 days; n (%)			

No. cardiologist visits; mean (sd)			
Electrocardiogram; n (%)			
No. electrocardiograms, mean (sd)			
No. distinct medication prescriptions; mean (sd)			
Use of glucose test strips; n (%)			
No. HbA1c tests ordered; mean (sd)			
No. glucose tests ordered; mean (sd)			
No. microalbuminuria tests ordered; mean (sd)			
No. creatinine tests ordered; mean (sd)			
No. BUN tests ordered, mean (sd)			
No. lipid tests; mean (sd)			

The table above shows our complete set of baseline characteristics. All comorbidities and previous acute conditions and previous utilization in the previous 12 months will be recorded. Age at index date will be calculated as the time difference between the index date and the patient's birth date. Identification of comorbidities and previous utilization will follow the following rules:

- Chronic comorbidities and previous acute conditions will be identified by occurrence of at least one ICD 9/10 for the respective condition in any position. See the additional workbooks titled "ICD 9 Dx Codes.xlsx" and "ICD 10 Dx Codes.xlsx" for a detailed list of ICD 9/10 codes that identify comorbidities.
- Previous healthcare utilization will be identified by occurrence of CPT or HCPCS codes for the respective form of utilization. See the additional workbooks "CPT codes.xlsx" and "HCSPCS codes.xlsx" for a detailed list of CPT and HCPCS codes.
- Previous prescription medications will be identified by occurrence of prescription filling with a medication's respective NDC or HCSPCS code. See additional workbook "NDC codes.xlsx" and "HCSPCS codes.xlsx" for a detailed list of relevant codes.

Also, given that we are comparing a branded agent against generic agent, we will perform exploratory instrumental variable analysis, in order to account for the confounding by indication. Some example of instrumental variables we can use and will explore the appropriateness of are:

- First three digits of zip code (ZIP3) and/or State
- National Provider Identifier (NPI)
- Index date and/or index quarter

9.3.1 Exposures

Exposure cohorts

- Treatment with empagliflozin (as add-on therapy to metformin)
- Treatment with a sulfonylurea (as add-on therapy to metformin)

9.3.2 Outcomes

9.3.2.1 Primary outcomes

Primary outcome

- First hospitalization for congestive heart failure (HHF) (we will first analyze this by looking at diagnosis code in any position, we will then run the analysis considering diagnosis coding in either the principal or secondary position).

The primary scope of the analysis will be limited to the primary outcome (hospitalization for HF), for which the study will be powered for, and limited to HCRU and cost outcomes. For all exploratory effectiveness outcomes outlined above, we will first examine the number of events, and incidence rate of the events in the follow-up for the unmatched cohort, before performing the final analysis, to evaluate feasibility of inclusion of these exploratory outcomes.

Clinical outcomes will be identified by occurrence of a combination of the ICD 9/10 for the respective condition and HCSPCS code. See additional workbooks "ICD 9 Dx Codes.xlsx" and "ICD 10 Dx Codes.xlsx" and "HCPSC codes.xlsx" for a detailed list of relevant ICD 9/10 codes and HCSPCS codes, respectively.

See sample results for the propensity score-matched population below:

Effectiveness Outcome	Metformin + Sulfonylurea(IR)	Metformin + Empagliflozin (IR)	Hazard Ratio (95% CI)
HHF			
MACE			
Myocardial infarction			
Stroke			
Coronary revascularization			
All-cause death			

Utilization Outcome (12 months post index date)	Metformin + Sulfonylurea (IR)	Metformin + Empagliflozin (IR)	Coefficient (95% CI)	P value
Hospitalizations				
LOS				
ED visits				
Outpatient visits				
Drug orders				
Total care costs				
Medical costs				

Pharmacy costs				

9.3.2.2 Secondary outcomes

Secondary outcomes

- Healthcare utilization outcomes: hospitalizations, emergency department (ED) visits, length of stay, number of filled drugs, outpatient visits
- All cause cost: Total cost of care, divided by medical (inpatient costs, outpatient costs, emergency costs) and pharmacy costs (all reported in Per Patient Per Month (PPPM) costs)

Exploratory outcomes

- Effectiveness outcomes: 2-point MACE as a Composite Score of myocardial infarction, stroke or coronary revascularization

9.3.2.3 Further outcomes

All pre-specified outcomes, which are not classified as primary or secondary, should be clearly identified as "further outcome" of interest and described as above.

9.4 DATA SOURCES

This study will utilize IQVIA's Real-World Data (RWD) Adjudicated Claims Database (formerly known as PharMetrics Plus). IQVIA's claims database is composed of more than 190 million unique enrollees from national and sub-national health plans and self-insured employer groups from 2006 to the present.[15] The database is considered representative of the sex and age demographics of the insured United States population.[16] The database contains a multitude of patient data points that are relevant for this study including:

- Demographic, geographic, and insurance type/enrollment information,
- Primary and specialty care visit dates and diagnosis codes,
- Medication use including refill dates, quantity, and days supplied, and
- Hospitalizations and emergency department visit dates, length of stay, and diagnosis codes

We anticipate having access to claims data that was generated though at least December 31, 2019. IQVIA's database has been extensively used in pharmacoepidemiological research. Recent examples include *Pandya et al.* (2020) and *Stolshek et al.* (2018).[16,17] The claims data will be fully de-identified prior to receiving access for analyses.

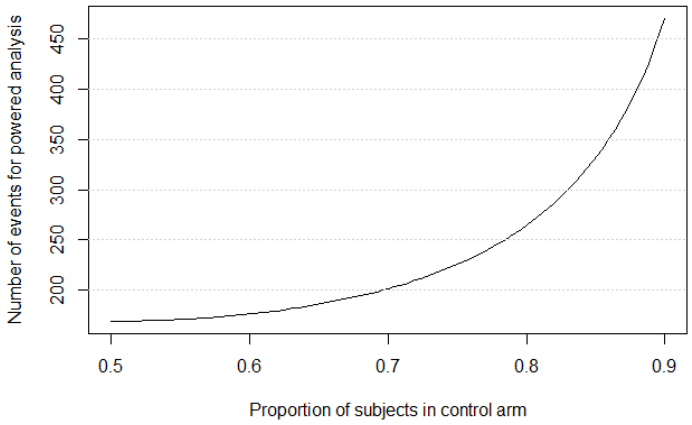
9.5 STUDY SIZE

The following calculation is intended to estimate the number of events necessary to perform a powered analysis of the effect of add-on treatment with empagliflozin on the incidence of

hospitalization from heart failure. We will use the formula below for the power calculation for a two-group survival analysis:

$$N_e = \frac{(Z_\alpha + Z_\beta)^2}{[\log(HR)]^2 q_0 q_1}$$

where the significance level, α, will be set equal to 5% and the type 2 error threshold, β, will be set equal to 20%, resulting in a Z_α and Z_β of 0.96 and 0.842, respectively. The EMPA-REG OUTCOME clinical trial reported a hazard ratio of 0.65 (=*HR*), which we have applied in our sample size calculation. Given that there will be substantially more control subjects than treatment subjects and assuming the application of IPTW would have the effect of balancing the cohorts, we consider a range of possible proportions of the control and treatment arms of the study. Below we visualize scenarios with a minimum and maximum proportion of patients in the control arm equal to 0.5 and 0.9, respectively. This corresponds to a minimum and maximum number of events required for a powered analysis of 169 and 470.



Next we must consider the potential incidence rates of hospitalization from heart failure in our study population and the implied number of patients needed in our sample. We note, first, that the EMPA-REG OUTCOME clinical trial reported incidence rates of 14.5 and 9.4 events per 1,000 patient years for the placebo- and empagliflozin-administered arms, respectively. We note, second, that our study population will be at high-risk of cardiovascular events similar to the EMPA-REG OUTCOME study population. Furthermore, using previously referenced evidence of the higher risk of cardiovascular events in sulfonylurea-treated patients we assume that the incidence rate is, at best, equal to that of the placebo-administered population of the EMPA-REG OUTCOME study.

A reasonable scenario might assume that 80% of our patients are in the control arm and use the estimated weighted average of the control and treatment arms (0.8×14.5 + 0.2×9.4 = 13.48) as the incidence rate and 265 events as the necessary number of events. This scenario would require 19,600 patient years available in the dataset.

Based on preliminary calculation stated below for IQVIA database, we believe there will be a sufficient sample size to conduct a powered analysis of the effect of empagliflozin use compared to either control arm. Nevertheless, the final decision of performing the analysis will

depend on the final sample size and the number of events accrued during the follow-up for primary outcome (*see key study outcomes section for details*)

Metformin Days Supply in PI	Empagliflozin Sample #	Metformin Sample size #
No Metformin	582	75,563
0 to 3 months	461	8,771
3 to 6 months	331	10,409
6 to 9 months	375	14,275
9 to 12 months	801	17,029
Total	**2550**	**126,047**
* The final sample will be different, based on further data cleaning and further application of inclusion/exclusion criteria		

9.6 DATA MANAGEMENT

PHEOR's data facility is in a secured building with a security guard presence twenty-four hours a day. The facility is monitored internally and externally with video and motion-based sensors with controlled access via keycard and keypad. Computing hardware is stored on racks in locked cabinets. Remote access is either via secure IP connection, with firewalls in PHEOR offices as well as the data center, or via software VPN. Servers run Linux and use standard file permissions and auditing systems to control and monitor access to restricted data files and directories. Staff workstations will use a password-protected screen-saver, set to activate automatically after 5 minutes of non-use; the screen saver will be automatically set whenever the computer is unattended for an extended period of time. All staff workstations have standard virus software installed and maintained with regular updates and patches.

Project staff will be the only researchers granted regular access rights to the data. The only other individuals with access are PHEOR's system administrators. These individuals are PHE employees and long-term contractors who have broad responsibilities across all of the company. One copy of each original database will be made as a backup and stored in a locked safe, in a locked office at PHEOR headquarters. Derived data and programs will be backed up to a second drive system located within the same secure data facility described above; this backup process can be turned off upon request.

Original data and backups will be destroyed on or before the date on which our authorized access to the restricted data ends or at the request of any vendors. There will never be any paper printouts of the data. Any electronic listing or log files will be treated as derived data as above.

9.7 DATA ANALYSIS

9.7.1 Main analysis

As described above starting with the initiation of treatment, we observe patient outcomes until one of:

- discontinuation or switch or addition of a drug in the comparator and/or other antihyperglycemic agents class
- occurrence(s) of an outcome of interest
- nursing home admission

- healthcare plan disenrollment
- exposure to other diabetes medications
- end of the study period

Step 1: Create the matched sample
There are many variants of propensity score matching. In the simplest version, individuals in the case group are matched 1:1 with individuals in the set of candidate controls, on the basis of similarity (minimized difference) of the propensity score, using a list-wise matching process (a list-wise matching process is one in which first a match for empagliflozin add-on patient 1 is found, then a match for case member 2, iterating to finding a match case group member N at the end of the matching procedure). In K-nearest neighbors matching, case group members are matched to the K members of the candidate set of controls (where K is a small positive number such as 2, 3 or 4), again based on minimized difference in propensity score. This method can be used if the initial data inspection determines that a larger sample size is required. It can improve the precision of estimates, but may result in additional bias due to poorer matches on average. In caliper matching (which may be applied to either nearest neighbor or K-nearest neighbor variants), individuals are selected for inclusion if their propensity score distance from the matching candidate is less than some caliper parameter, c (for estimating means or risk differences, often caliper width equaling 0.2 of the standard deviation of the logit of propensity score is used for estimating risk differences or differences in means). If no acceptable match is found within the caliper, the case is dropped. Caliper matching may be required if it is necessary to ensure that all matches meet some minimally acceptable threshold for match quality; however, it may further reduce the generalizability of study findings by dropping large numbers of cases.
The nearest neighbor and K-nearest neighbor algorithms are typically implemented without replacement, meaning that when control candidate *i* has been selected as a match for case member 1, he/she is no longer available as a match candidate for case member 2. In this arrangement, the order in which the matching is implemented across patients will affect the quality of the overall match. For example, if individuals are first ranked by age, a slightly different result will be obtained than if individuals are first ranked by decreasing propensity score.
The study team will select a specific propensity score matching method following a thorough inspection of the analytic dataset. If the sample sizes for cases and controls are large enough we will consider using nearest neighbor with caliper matching. If this is not the case or if this approach fails to find a match for a large number of empagliflozin add-on patients (>10% of the cases fail to match), we will loosen the caliper width to up to 0.6 (where bias reduction is still up to >90%). Alternatively, if we are unable to find a good match for over 10% of the cases even after loosening the caliper width to 0.6, we will consider using matching with replacement. If we are still unable to match an acceptable number of cases, we will implement inverse probability of treatment weighting (IPTW), which allows for complete inclusion of the cases.
Following the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) best practices, [70] as a validation measure we will examine whether there are large differences in observed attributes (covariate values) of the empagliflozin add-on patientsand the reweighted control group by assessing visual tools, such as density balance plots, and standardized mean differences. We will determine that the covariates are well-balanced if standardized mean differences do not exceed 10%. These analyses will serve as tools for assessing the quality of the matching procedure.

Step 2: Calculate descriptive statistics
We will then use our matched cohorts to calculate descriptive statistics of the baseline characteristics of our patient population (separately for the empagliflozin cohort, the sulfonylurea cohort, and the overall population). After calculation of standardized mean differences, chi-square tests will be used to assess statistically significant differences for categorical variables, and t-tests will be used to assess statistically significant differences for continuous variables.

Step 3: Construct statistical models of primary and secondary outcomes
Using observed safety and effectiveness events, we will calculate incidence rates and 95% confidence intervals for IPTW/PSM matched cohorts. We will estimate the hazard ratios and confidence intervals via Cox regression for primary outcome of interest, comparing empagliflozin vs. comparison group. We will also estimate differences in healthcare utilization using incident counts, by performing either Poisson or negative binomial regression, and differences in cost outcomes will be assessed by generalized linear regression using a Gamma family log link function.

9.7.2 Further analysis

Sensitivity analyses:

- Exploratory analysis of the feasibility of an instrumental variable model, using any of the previously identified potential instruments
    - Conditional on feasibility, an instrumental variable model would be implemented
    - Our proposed instrumental variables are all in the "preference" format. For example, geographic preference of the *j*-th geographic zone (for example, Zip3) would be calculated as:
        - $Z_j = \frac{Count\ of\ metformin+sulfonylureapatients\_i}{Count\ of\ metformin+empagliflozin\ patients\_i}$
        - Here the *i*-th patient's prescribed treatment is left out of the calculation. All variables of this format should 1) be correlated with our treatment indicator, and 2) be independent of patient outcomes.
- CVD-related death, defined as death occurring within 30 days after diagnosis for MI, stroke, unstable angina, heart failure, etc. (note: deaths that occurred in the hospital identifiable in claims data)

9.8 QUALITY CONTROL

PHEOR implements best practices and procedures for ensuring data quality. The following quality assurance and quality control measures are applied to all programming that executes data extraction and transformation:

- Check program logs for notes, warning messages, and errors
- Check derived data values against source data for a patient sample to ensure correct derivation

- Verify that variables needed to support tables/listings/figures are found in the derived data set
- Check that data fields are not truncated
- Check data points for values outside expected ranges, where appropriate
- Check that data are rounded correctly and in accordance to the analysis plan
- Check that abbreviations, range categories, and subgroups conform to the analysis plan
- Ensure the consistency of sample counts across relevant tables/listings/figures
- Check formats consistent with the analysis plan
- Ensure no typos, misspellings, or false values
- Check that summary statistics are correct; check at least one category in each summary table against the data listings
- Check that data are in accordance with the Data Plan
- Check that subgroups conform to the Data Plan
- Check that mathematical algorithms specified in the Data Plan and Analysis Plan have been implemented correctly
- Ensure there are no duplicate observations

Additionally, the development and QC process involves understanding of the technical specifications (Data Plan/Analysis Plan) with regards to the protocol, so that the programming carries out the intent of the study.

9.9 LIMITATIONS OF THE RESEARCH METHODS

- Inferior level of internal validity compared to prospective study
- Study sample does not represent patient population covered by Medicare, as commercially-insured population is meaningfully different from overall U.S. patient population
- Subject to confounding, i.e. confounding variables may account for treatment with empagliflozin.
- Relevant patient variables (e.g. HbA1c lab values, creatinine lab values, socioeconomic status) are not available
- Necessary to assume accurate recordkeeping/reporting of patient characteristics, treatments, and clinical/economic outcomes

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

See Section 9.8.

9.10.2 Study records

Not applicable

9.10.2.1 Source documents

Not applicable

9.10.2.2 Direct access to source data and documents

The investigator/institution will permit study-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents

9.10.3 Protocol deviations

Consult with the NIS Statistician/PSTAT/PSTAT-MA on protocol deviations.

10. PROTECTION OF HUMAN SUBJECTS

Not applicable

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

Not applicable

10.2 STATEMENT OF CONFIDENTIALITY

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

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

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable based on secondary use of data without the potential that any employee of BI or agent working on behalf of BI will have access to patient-level data.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Include any plans for submission of progress reports and final reports; any arrangements made between marketing authorisation holders for the disseminating and communicating study results of Joint PASS, if applicable.

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

13. REFERENCES

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

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

Number	Document Reference Number	Date	Title
1	<Number>	<dd mmm yyyy>	ICD 9 Dx Codes
2	<Number>	<dd mmm yyyy>	ICD 9 Proc Codes
3	<Number>	<dd mmm yyyy>	ICD 10 Dx Codes
4			ICD 10 Proc Codes
5			CPT Codes
6			HCSPCS Codes
7			NDC Codes

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

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

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

In question 9.5 of the Checklist, Revision 1:

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

ANNEX 3. ADDITIONAL INFORMATION

Additional annexes may be included if necessary.

ANNEX 4. REVIEWERS AND APPROVAL SIGNATURES

The NIS Protocol must be sent for review to the following individuals **prior to approval**.

Reviewer	**NIS involving BI product(s)**	**NIS not involving BI product(s)**	
		Global NIS	**Local NIS**
NIS Lead	X	X	X
Global TM Epi	X	X	X
Global TMM / TMMA / TM Market Access	X	X	
Global Project Statistician	X	X	
Global TM RA	X		
Global PVWG Chair	X		
GPV SC	X	X	X
Global CTIS representative	X		
Local Medical Director	X (if local study)		X
Local Head MAcc / HEOR Director	X (if local study)		X
Global TA Head Epi*	X	X	
Global TA Head Clinical Development / Medical Affairs / Market Access*	X	X	
Global TA Head PV RM*	X		
RWE CoE	X	X	
PSTAT / PSTAT-MA (for NISnd only)	X	X	X
NIS DM	X	X	X
Local Head MA/Clinical Development			X (does not apply to NISed without chart abstraction)

** After review by Global TM for function*

*Include this Annex if signatures of external investigators are required **and/or** for studies that will not be stored in the DMS for submission documents. For non-interventional studies approval signatures must be obtained from the individuals as noted in section 5.1.3 "Manage NIS Protocol" in the corresponding SOP 001-MCS-90-118. If the study is a PASS, additional approvals are necessary; refer to SOP 001-MCS-90-140 "Post Authorization Safety Studies".*

Study Title:

Study Number:

Protocol Version:

I herewith certify that I agree to the content of the study protocol and to all documents referenced in the study protocol.
Note: Please insert respective signatories with regard to the SOP.

Position: ___PI_ Name/Date: <Lukas Müller /dd mmm yyyy> Signature**:** _____

Position: NIS Lead Name/Date: <Julia Becker/ dd mmm yyyy> Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____