Boehringer Ingelheim

# Protocol for non-interventional studies based on existing data

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| **Document Number:** | **c28125444-03** |
| **BI Study Number:** | 1245-0194 |
| **BI Investigational Product(s):** | Empagliflozin (Jardiance®)<br>Empagliflozin + Linagliptin (Glyxambi®)<br>Empagliflozin + Metformin (Synjardy®) |
| **Title:** | **Cardiovascular outcomes, and mortality in Danish patients with type 2 diabetes who initiate empagliflozin versus Glucagon-Like Peptide-1 Receptor Agonists (GLP1-RA): A Danish nationwide comparative effectiveness study [EMPLACE™]** |
| **Brief Lay Title:** | A Study Using Medical Records of Danish People with Type 2 Diabetes Comparing Empagliflozin and Glucagon-Like Peptide-1 Receptor Agonists (GLP1-RA) in the Occurrence of Serious Cardiovascular Outcomes |
| **Protocol version identifier:** | 3.0 |
| **Date of last version of protocol:** | 08 November 2021 |
| **PASS:** | No |
| **EU PAS register number:** | EUPAS29985 |
| **Active substance:** | A10BX12 Empagliflozin<br>A10BK03 Empagliflozin<br>A10BD19 Empagliflozin + Linagliptin<br>A10BD20 Empagliflozin + Metformin<br><br>GLP1-RAs:<br>A10BJ01, A10BX04 (Exenatide)<br>A10BJ02, A10BX07 (Liraglutide)<br>A10BJ03, A10BX10 (Lixisenatide)<br>A10BJ05, A10BX14 (Dulaglutide)<br>A10BJ06 (Semaglutide)<br>A10AE56 (Insulin glargin + Liraglutide)<br>A10AE54 (Insulin glargin + Lixisenatid) |

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| **Medicinal product:** | Jardiance<br>Glyxambi<br>Synjardy<br>Bydureon<br>Victoza<br>Lyxumia<br>Trulicity<br>Ozempic<br>Rybelsus<br>Xultophy<br>Suliqua |
| **Product reference:** | Empagliflozin (Jardiance®): EMEA/H/C/002677<br>Empagliflozin + Linagliptin (Glyxambi®): EMEA/H/C/003833<br>Empagliflozin + Metformin (Synjardy®): EMEA/H/C/003770<br>Exenatide (Bydureon®): EMEA/H/C/002020<br>Liraglutide (Victoza®): EMEA/H/C/001026<br>Lixenatide (Lyxumia®): EMEA/H/C/002445<br>Dulaglutide (Trulicity®): EMEA/H/C/002825<br>Semaglutide (Ozempic®, Rybelsus®): EMEA/H/C/004174, EMEA/H/C/004953<br>Insulin glargin + Liraglutide (Xultophy®): EMEA/H/C/002647<br>Insulin glargin + Lixenatide (Suliqua®): EMEA/H/C/004243 |
| **Procedure number:** | Not applicable |
| **Joint PASS:** | No |
| **Research question and objectives:** | To compare, among patients with type 2 diabetes in Denmark, clinical outcomes among new users (initiators) of empagliflozin versus GLP1-RA. |
| **Country(-ies) of study:** | Denmark |
| **Authors:** | [redacted]<br>On behalf of the [redacted] |
| **Marketing authorisation holder(s):** | [redacted] |

| | |
|---|---|
| | [redacted] |
| **MAH contact person:** | [redacted] |
| **Date:** | 08 November 2021 |
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# 1. TABLE OF CONTENTS

# 2. LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AUC | Area under the Curve |
| CI | Confidence Interval |
| CML | Local Clinical Monitor |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTMF | Clinical Trial Master File |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| DMC | Data Monitoring Committee |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EudraCT | European Clinical Trials Database |
| FAS | Full Analysis Set |
| GCP | Good Clinical Practice |
| HCRU | Health Care Resource Use |
| [redacted] | |
| IB | Investigator's Brochure |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| ISF | Investigator Site File |
| i.v. | intravenous |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web-based Response System |
| LABKA | The clinical laboratory information system (LABKA) research database at [redacted] |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| MST | Medical Subteam |
| OPU | Operative Unit |
| p.o. | per os (oral) |
| PCC | Protocol Challenge Committee |
| q.d. | quaque die (once a day) |
| SAE | Serious Adverse Event |
| s.c. | subcutaneous |
| SPC | Summary of Product Characteristics |
| TCM | Trial Clinical Monitor |
| TDMAP | Trial Data Management and Analysis Plan |
| t.i.d. | ter in die (3 times a day) |
| TMM | Team Member Medicine |
| TMW | Trial Medical Writer |
| TSAP | Trial Statistical Analysis Plan |

# 3. RESPONSIBLE PARTIES

FROM THE [redacted]:

Senior epidemiologist:
[redacted]

Statisticians: [redacted] Team Pharmacoepi:
[redacted] was employed at [redacted] during first protocol and study phase) [redacted] (until May 2021)
[redacted] (from August 2021)
[redacted] (until 2020)

[redacted] of department, Principle investigator:
[redacted]

Epidemiologist:
[redacted] (was employed at [redacted] during first protocol and study phase; from 2021 employed at [redacted]

FROM BOEHRINGER INGELHEIM

[redacted]

[redacted] (from August 2021)

[redacted]

[redacted] (until 2020)

[redacted]

[redacted] (from August 2021)

[redacted] (from August 2021)

# 4. ABSTRACT

| | | | |
|---|---|---|---|
| **Name of company:**<br>Boehringer Ingelheim | | | |
| **Name of finished medicinal product:**<br>Empagliflozin:<br>A10BX12, A10BK03, A10BD19, A10BD20<br>GLP1-RAs:<br>A10BJ01, A10BX04, A10BJ02, A10BX07, A10BJ03, A10BX10,<br>A10BJ05, A10BX14, A10BJ06, A10AE56, A10AE54 | | | |
| **Name of active ingredient:**<br>See above | | | |
| **Protocol date:**<br>15JUL2018 | **Study number:**<br>1245-0194 | **Version/Revision:**<br>3.0 | **Version/Revision date:**<br>08NOV2021 |
| **Title of study:** | **Cardiovascular outcomes, and mortality in Danish patients with type 2 diabetes who initiate empagliflozin versus Glucagon-Like Peptide-1 Receptor Agonists (GLP1-RA): A Danish nationwide comparative effectiveness study [EMPLACE™]** | | |
| **Rationale and background:** | Utilization of the glucose-lowering drugs Glucagon-Like Peptide 1 Receptor Agonists (GLP1-RA) and Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors has increased substantially in people with type 2 diabetes (T2D) worldwide. Trials have shown that the GLP1-RA liraglutide and the SGLT2 inhibitor empagliflozin caused (13% and 14%, respectively) reductions in major adverse cardiac events among T2D patients with high cardiovascular risk, with similar reductions in HbA1c of 0.4% and 0.3%. Little is known about how these therapies compare regarding clinical outcomes in routine clinical care. In Denmark, nationwide population-based databases holding individual-level patient data enable comparative effectiveness studies among non-selected patients with T2D. | | |
| **Research question and objectives:** | Our primary objective is to compare clinical outcomes (cardiovascular outcomes, and mortality) among empagliflozin initiators and GLP1-RA initiators in Denmark | | |
| **Study design:** | Non-interventional cohort study using existing data. The study will use a new user design and compare new users of empagliflozin with new users of GLP1-RA. | | |
| **Population:** | The study population will include all eligible patients with T2D initiating treatment with empagliflozin or with GLP1-RA in 2015-2020. | | |

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| **Name of active ingredient:**<br>See above | | | |
| **Protocol date:**<br>15JUL2018 | **Study number:**<br>1245-0194 | **Version/Revision:**<br>3.0 | **Version/Revision date:**<br>08NOV2021 |
| **Variables**: | *Exposure*: Patients will be included on the index date of their first prescription for empagliflozin or GLP1-RA, respectively (either as monotherapy or fixed-dose combination with another drug), with or without treatment with other GLDs. Patients with previous use of any SGLT2i or GLP-1RA at any time before treatment initiation will be excluded. We will also exclude patients prescribed liraglutide with the brand-name Saxenda® (liraglutide 3.0 mg daily, approved as a treatment for obesity in 2015).<br>*Outcomes*: The primary outcome in our study will be a composite of hospitalization due to stroke, myocardial infarction, unstable angina, coronary revascularization, hospitalized heart failure (HHF), or all-cause death (expanded MACE). Secondary outcomes will be inpatient hospital admission with a diagnosis of HF and/or initiation of community prescription drug therapy with loop diuretics; inpatient hospital admission with a diagnosis of HF and/or all-cause death; composite of all-cause hospitalization or death; all-cause hospitalization; all-cause death, and hospitalization for HF.<br>Hospitalization will be defined as any inpatient hospital admission at any Danish hospital, independent of admissions being through emergency room contact, by ambulance, self-referral, or via referral from GP, outpatient clinic, or other health care provider.<br>In further analyses, we will examine total health care resource use associated with empagliflozin or GLP1-RA, including total inpatient days, length-of-stay of patients with admissions, total hospital specialist outpatient clinic services provided, total cost of hospital care, total general practitioner services provided in primary care and their costs, total drug prescription use and pharmacy costs, and total medical costs.<br>*Confounders*: Age, gender, year of inclusion, diabetes duration, number of diabetes drugs used, metformin use, insulin use, diagnoses of retinopathy, neuropathy, or nephropathy, estimated glomerular filtration rate (eGFR), | | |

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| **Name of active ingredient:**<br>See above | | | |
| **Protocol date:**<br>15JUL2018 | **Study number:**<br>1245-0194 | **Version/Revision:**<br>3.0 | **Version/Revision date:**<br>08NOV2021 |
| | history of ischemic heart disease, cerebrovascular disease, peripheral vascular disease, heart failure (further divided by duration and primary/secondary diagnosis) ), rheumatological disease, dementia, osteoporosis, medical obesity, chronic obstructive pulmonary disease, cancer, use of angiotensin-converting-enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs), other antihypertensives, statins, antiplatelet drugs, social and frailty markers, marital status, prescriptions for mental disorders, alcoholism, and number of prior hospital admission days and other prior HCRU. | | |
| **Data sources:** | Danish population-based linked registries: The Civil Registration System, The Danish National Patient Register, The National Database of Reimbursed Prescriptions, The LABKA Database | | |
| **Study size:** | Source population: Approx. 0.5 mill. patients with drug-treated type 2 diabetes in Denmark, during the period 1994-2020. The study size will be driven by the uptake of empagliflozin following its approval and launch in Denmark, with rapid increase after 2015. In 2016 there were 13,362 users of SGLT2 inhibitors in Denmark, including approximately 6,000 users of empagliflozin. In 2016, there were 24,273 users of GLP-1 receptor agonists, including 23,420 users of GLP1-RA | | |

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| **Name of active ingredient:**<br>See above | | | |
| **Protocol date:**<br>15JUL2018 | **Study number:**<br>1245-0194 | **Version/Revision:**<br>3.0 | **Version/Revision date:**<br>08NOV2021 |
| **Data analysis:** | We will provide two approaches in our study across the two exposure groups: an on-treatment (OT) exposure definition, and an intention-to-treat (ITT) exposure definition (see section 9.1 for details). For balanced comparison of the two treatment groups, we plan to conduct propensity score (PS) balancing of potential confounders (see section 9.3, covariates) across the two treatment groups. Covariate balance will be assessed by checking standardized differences (SD) between the groups; a covariate being considered well balanced if the SD is below 0.1. We will use Cox regression analyses to compute crude and adjusted hazard ratios (HRs) with 95% CIs to examine the association between empagliflozin versus GLP1-RA initiation and study outcomes. For each of the primary outcomes (primary objective) and secondary outcomes (secondary objective) of interest, estimation of adjusted use HRs for time from "index date" until the defined (first) event or the end of the follow-up period with 95% CIs will be considered the main analysis.<br>[redacted] | | |
| **Milestones:** | Final Protocol: 15 July 2018<br>First interim analysis: 2017 data<br>Second interim analysis: 2018 data<br>Protocol version 2.0: 22 October 2020<br>Protocol version 3.0: 08 November 2021<br>Third interim analysis (year 2019 data): Expected December 2021<br>Final analysis (year 2020 data) including HCRU: Expected December 2021 | | |

# 5. AMENDMENTS AND UPDATES

| Number | Date | Section of study protocol | Amendment or update | Reason |
|---|---|---|---|---|
| 1 | 22 October 2020 | Milestone | Update | Interim report and amendment specifications |
| 2 | 22 October 2020 | Rationale and background | Amendment | GLP1-RA class analysis specified incl rationale for liraglutide in the first 2 interim reports. |
| 3 | 22 October 2020 | Research and objectives | Amendment | GLP1-RA class analysis specified |
| 4 | 22 October 2020 | Study design | Update<br><br>Amendment | Outcome clarification<br>Stratifiers listed<br>GLP1-RA class analysis specified |
| 5 | 22 October 2020 | Study population | Update<br><br>Amendment | Population description clarified<br>GLP1-RA class analysis specified |
| 6 | 22 October 2020 | Study period | Update | Clarified to include data capture from entire contracting period (end 2020. expected to be available end 2021) |
| 7 | 22 October 2020 | Lookback | Update | Clarified description of lookback period |

| Number | Date | Section of study protocol | Amendment or update | Reason |
|---|---|---|---|---|
| 8 | 22 October 2020 | Inclusion/ Exclusion | Amendment | GLP1-RA class analysis specified<br>Define analysis restrictions related to +/- previous events |
| 9 | 22 October 2020 | Follow up | update | Grace period and treatment duration description clarified |
| 10 | 22 October 2020 | Outcome | Update | Cardiovascular event definitions updated |
| 11 | 22 October 2020 | Covariates | Update | Updated list of covariates |
| 12 | 22 October 2020 | Data Source | Update | Clarified description of data sources incl lab data |
| 13 | 22 October 2020 | Study size | Update | Included information on most recent T2D and new user proportions and estimated 2020 pers exposure/pers yrs. |
| 14 | 22 October 2020 | Data analysis | Update | IIT and OT, PS and multivariate model as well as IPWT description clarified.<br>Strata list updated |
| 15 | 22 October 2020 | Abstract pages | Update | Updated according to the relevant section updates/amendments |

| Number | Date | Section of study protocol | Amendment or update | Reason |
|---|---|---|---|---|
| 16 | 08 November 2021 | | Amendment | Amended HCRU endpoint definitions |
| 17 | 08 November 2021 | Milestones | Update | Update of milestone achievements and expected dates |
| 18 | 08 November 2021 | Responsible parties | Update | New members of team |
| 19 | 08 November 2021 | Study Outcomes | Amendment | Study outcome on main analysis is still the same. HCRU analysis added and will be described in SAP |
| 20 | 08 November 2021 | Follow up | Update | Grace period changed to 30 days |

# 6. MILESTONES

| Milestone | Planned Date |
|---|---|
| Protocol version 1.0 | 15 July 2018 |
| Start of data collection | 01 January 2015 |
| End of data collection | December 2021 |
| Interim report 1 | April 2019 (EASD abstract) / August 2019 (EASD Poster) |
| Protocol version 2.0 | 22 October 2020 |
| Interim report 2 | Manuscript May 2021 |
| Protocol version 3.0 | 08 November 2021 |
| Interim report 3 | December 2021 |
| Registration in the EU PAS register | 04 June 2019<br>(http://www.encepp.eu/encepp/viewResource.htm?id=37726) |
| Final report of study results: | Q4 2021 including HCRU |

# 7. RATIONALE AND BACKGROUND

Utilization of the newer type 2 diabetes (T2D) medications GLP1 RA and SGLT2 inhibitors in Denmark has increased substantially, after clinical trials have provided evidence that these drugs reduce cardiovascular disease (CVD) risk beyond their glucose-lowering effect. For example, in the LEADER and EMPA-REG OUTCOME trials (6,7), the GLP1 RA liraglutide and the SGLT2 inhibitor empagliflozin caused (13% and 14%, respectively) reductions in major adverse cardiac events (MACE; i.e., CVD death, myocardial infarction, or stroke) among T2D patients, with reductions in HbA1c of 0.4% and 0.3%, respectively. Since GLP1 RA and SGLT2 inhibitors furthermore both are associated with weight loss and low risk of hypoglycemia, they have become a popular choice for second-line therapy, in particular as add-on therapy to metformin. In Denmark, liraglutide has been the overwhelmingly used GLP1 RA since 2010 (8), while use of exenatide has remained low; use of lixisenatide and dulaglutide is still low as of 2016 (9). The initial 2 interim analyses of this study were restricted to comparison of empagliflozin versus liraglutide as this active medical compound was the single most frequently used GLP-1-RA in DK between 2015-2018. For the final analysis (between 2015-2020) the GLP1RA class will be used as the comparator to include new GLP1-RA products in the evaluation of the GLP1-RA class. Regarding SGLT2 inhibitors in Denmark, dapagliflozin has been the clearly most used SGLT2 inhibitor up to 2015 (10), whereas from 2016 onwards the use of empagliflozin has increased substantially (use of canagliflozin has generally been low) (9).

Little is known about the differences in patient characteristics between users of GLP1-RA versus users of empagliflozin, and how these therapies compare regarding clinical outcomes in routine clinical care. In Denmark, nationwide population-based databases holding individual-level patient data enable drug utilization studies and comparative effectiveness studies in clinical practice among non-selected patients with T2D (10,11). In an ongoing collaboration between Boehringer Ingelheim and the [redacted] in [redacted], we investigate patient characteristics at the time of empagliflozin initiation, and compare the characteristics with those of initiators of other frequently used newer glucose-lowering drugs, namely: SGLT2 inhibitors other than empagliflozin, GLP-1 RA, and DPP-4 inhibitors. Our preliminary results suggest that initiators of empagliflozin and GLP-1 RA in Denmark are very similar regarding demographic and clinical variables and baseline glycemic control. We now propose to conduct a cohort study of cardiovascular outcomes and mortality in Danish patients with T2D who initiate empagliflozin versus GLP1-RA.

# 8. RESEARCH QUESTION AND OBJECTIVES

The primary research question is to evaluate whether, among patients with T2D, initiation of empagliflozin changes the adjusted incidence of outcomes compared with initiation of GLP1-RA.

For the above study outcomes, "inpatient hospital admission" in the Danish registries covers all types of hospital entry, for example; admission via emergency room entrance, admission by ambulance, self-referral, referral from GP/primary health care provider.

[redacted]

# 9. RESEARCH METHODS

## 9.1 STUDY DESIGN

Non-interventional cohort study using existing data.

We will use two alternative analytic approaches in our study: an on-treatment (OT) exposure definition, and an intention-to-treat (ITT) exposure definition. For the OT analyses, treatment duration will be based on the estimated number of days covered by each filled prescription, calculated as the number of packages * the numerical volume of a package. A grace period of 30 days will be added. In the OT analysis, participants are censored from further follow-up at either treatment cessation, initiation of an alternative drug in the study drug class (for example, dapagliflozin among empagliflozin users), and initiation of a drug from the comparator study drug class (for example, liraglutide or another GLP-1RA among empagliflozin users). Addition of other GLD classes are allowed.

For the ITT analyses, participants are defined as exposed from the start of treatment throughout follow-up, analogous to an ITT design in a clinical trial.

In both analyses, participants will be followed from the date of initiation of empagliflozin or GLP1-RA treatment until outcome event, date of death, emigration, or end of study at December 31, 2020 or last data availability (or, in the OT analyses, also until treatment cessation or drug changes as explained above). In the analyses of the composite outcomes, patients are censored at the first occurrence of any outcome-defining event. For individual outcomes, patients are censored at the first occurrence of the outcome analyzed, independent of other outcomes. We will construct adjusted cumulative incidence curves for the different outcomes, taking competing risk of death into account when examining non-fatal outcomes. We will use Cox proportional hazards regression with time since treatment initiation as the underlying timescale to compute adjusted hazard ratios (aHRs) with 95% CIs. We will repeat all outcome analyses among empagliflozin vs. GLP1-RA initiators stratified by different baseline characteristics, i.e. by applying propensity score balancing of potential confounders across the two treatment groups within strata of sex, age (=65 years), presence or absence of cardiovascular disease at baseline (ischemic heart disease, HF, cerebrovascular disease, or peripheral vascular disease), current insulin use, current metformin use, and calendar periods before and after publication of the EMPA-REG OUTCOME and LEADER CVOTs (current analysis Jan 2015 – June 2016, July 2016 – Dec 2018).

## 9.2 SETTING

### 9.2.1 Study population

The source population for our study consists of individuals with T2D, who are defined in our study as individuals who live in Denmark and have ever used oral antihyperglycemic drugs or insulin (ATC-codes A10A, A10B) between 1994-2020, defined as one or more prescriptions for: metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, insulin, alfa-glucosidase inhibitors, other oral antihyperglycemic drugs, or combination products, according to the Anatomical Therapeutic Chemical (ATC)

classification system (12). Diabetic patients who under the age of 30 used insulin as monotherapy and never used oral antihyperglycemic medications will be excluded as likely T1D patients (2,13). Within this source population, we will identify our study population of adult type 2 diabetes patients initiating empagliflozin or GLP1-RA between 2015-2020.

The use of hospital ICD codes recorded in the Danish National Patient Register to identify patients with diabetes excluding gestational diabetes can only identify diabetes patients who required hospital treatment and treatment by hospital-based specialist doctors. Uncomplicated type 2 diabetes is usually treated by general practitioners (i.e., ~80% of type 2 diabetes patients are followed mainly in primary care), and thus not completely registered in hospital registries (14). The sensitivity of the Danish National Patient Register in identifying patients with known diabetes through diabetes diagnosis codes has been estimated at 64% (as most people with diabetes have hospital contact at some point of time), while the PPV of a diabetes diagnosis in the same Register is 97% (15). In comparison, the sensitivity of the Danish National Prescription Registry in identifying patients with diabetes through one or more glucose-lowering drug prescriptions has been estimated at 72% (as not all diabetes is drug treated), while the PPV of one glucose-lowering drug prescription for presence of diabetes is 95% (15). In the case of the present study all patients redeeming a prescription for the drugs examined will be registered with the Danish National Prescription Registry (16). Empagliflozin and GLP1-RA are prescribed/started as initial drug both by general practitioners (GPs) and specialist physicians in Denmark, and most of the follow-up prescriptions (for chronic treatment) will be issued by GPs or primary care physicians. All these prescriptions, no matter which physician prescribed them, are dispensed and registered on the individual level at essentially monopolized community pharmacies in Denmark, and therefore, new user data for the drugs is complete on the national level.

### 9.2.2 Study period

The planned study period is 1 January 2015 to 31 December 2020. Empagliflozin was launched in Denmark August 2014.

### 9.2.3 Index prescription definition

The index prescription will be the first prescription for the study medication of interest that fulfils the definition of new user during the study period. Index prescriptions/dispensings of the study drugs include the single study drugs or fixed-dose combinations of the study drugs with other glucose-lowering drugs.

### 9.2.4 Index date

The index date will be defined as the date on which each identified new user receives the index prescription for empagliflozin or GLP1-RA.

### 9.2.5 Baseline and lookback period

To characterize the empagliflozin and GLP1-RA cohorts at the time of study drug initiation, all information available during the lookback (pre-index) time period will be collected. The lookback time period is defined as the time period ending on the index date. All cohort

members are required to have at least 12 months of data history before the index date (baseline period), the lookback period will therefore include at least 365 days during which covariates can be evaluated. For most cohort members, more data on covariates is available beyond 365 days. Thus, the look-back period for co-medication will be 365 days and up to 15 years for chronic co-diagnoses.

### 9.2.6 Inclusion criteria

All patients will be required to meet all of the following criteria:

- Be aged 18 or more years at the index date (date of initiation of empagliflozin or GLP1-RA).
- Have at least 12 months of residency in Denmark prior to the index date.
- Have T2D ever before the index date (defined in detail under study population)

The empagliflozin-exposed population must also meet the following criteria:

- Have at least one prescription for empagliflozin or fixed-dose combination of empagliflozin with another drug, with or without treatment with another glucose-lowering drug.
- Have no prescription/dispensing of SGLT2 inhibitors (including empagliflozin) alone or in fixed-dose combination prior to the index date.
- Have no prescription/dispensing of a GLP-1 RA alone or in fixed-dose combination prior to the index date.

The population exposed to GLP1-RA must meet the following criteria:

- Have at least one prescription for GLP1-RA or a fixed-dose combination of GLP1-RA with another drug, with or without treatment with another glucose-lowering drug.
- Have no prescription/dispensing of a GLP-1 receptor agonist alone or in fixed-dose combination prior to the index date.
- Have no prescription/dispensing of SGLT2 inhibitors (including empagliflozin) alone or in fixed-dose combination prior to the index date.

### 9.2.7 Exclusion criteria

Patients with type 1 diabetes T1D before the index date will not be included in the study.

In general, analysis will include patients with previous outcome events, and adjustment for the history of these events will be carried out in the regression models rather than excluding them (e.g. assess outcome rates of myocardial infarction in empagliflozin and GLP1-RA initiators while adjusting for previous history of myocardial infarction, unstable angina, or coronary revascularization) to asses first event after SGLT2 or GLP1-RA initiation. However, an analysis of a composite of first incident HHF or first initiation of loop diuretic therapy will be restricted to patients with no previous HHF or loop-diuretic use.

### 9.2.8 Follow-up of subjects

Follow-up will start the day after the index date, which will be the date of the first prescription for empagliflozin or GLP1-RA including the index date.

For the analysis of each outcome, follow-up time in a given cohort in a given exposure category for each patient will end at whichever of the following dates occurs first:

- The date of the outcome event; acute hospital admission with heart failure (or initiation of loop diuretics), stroke, myocardial infarction, unstable angina, or coronary revascularization, or all-cause acute hospital admission
- The date of death.
- The date of study end.
- The emigration date out of Denmark.

For the OT analyses, treatment duration will be based on the estimated number of days covered by each filled prescription, calculated as the number of packages * the numerical volume of a package. A grace period of 30 days will be added. In the OT analysis, participants are censored from further follow-up at either treatment cessation, initiation of an alternative drug in the study drug class (for example, dapagliflozin among empagliflozin users), and initiation of a drug from the comparator study drug class (for example, liraglutide or another GLP-1RA among empagliflozin users).

For the ITT analyses, participants are defined as exposed from the start of treatment throughout follow-up, analogous to an ITT design in a clinical trial.

Follow-up will not be censored if glucose-lowering drugs other than the index drugs are prescribed in addition to empagliflozin or GLP1-RA after the index date.

## 9.3 VARIABLES

### 9.3.1 Exposures

For this study, eligible patients will be identified from prescription/dispensing for the study medications of interest listed in the Danish prescription registries:

A10BX12 (Empagliflozin (Jardiance®))
A10BK03 (Empagliflozin (Jardiance®))
A10BD19 (Empagliflozin + Linagliptin (Glyxambi®))
A10BD20 (Empagliflozin + Metformin (Synjardy®))

GLP1-RAs:
A10BJ01, A10BX04 (Exenatide (Bydureon®)
A10BJ02, A10BX07 (Liraglutide (Victoza®)
A10BJ03, A10BX10 (Lixisenatide (Lyxumia®)
A10BJ05, A10BX14 (Dulaglutide (Trulicity®)
A10BJ06 (Semaglutide (Ozempic® Rybelsus®)
A10AE56 (Insulin degludec + Liraglutide (Xultophy®)
A10AE54 (Insulin glargin + Lixisenatid (Suliqua®)

### 9.3.2 Study outcomes

The primary outcomes of interest for this study are the time from "index date" until (first) event of cardiovascular outcomes and mortality.

*Primary study outcome:*

- "Expanded MACE": All-cause death, acute admission with non-fatal (within 30 days) stroke, acute admission with non-fatal (within 30 days) MI, admission with unstable angina, coronary revascularization, or acute admission with non-fatal HF

*Secondary outcomes of interest:*

- Inpatient hospital admission with a diagnosis of HF and/or initiation of community prescription drug therapy with loop diuretics
- Inpatient hospital admission with a diagnosis of HF and/or all-cause death
- Composite of all-cause hospitalization or death
- All cause hospitalization
- All-cause death
- Hospitalization for HF

For the above study outcomes, "inpatient hospital admission" in the Danish registries covers all types of hospital entry that lead to inpatient admission, for example; admission via emergency room entrance, admission by ambulance, self-referral, and referral from GP/primary health care provider. Major cardiovascular outcomes such as myocardial infarction or acute heart failure almost always lead to inpatient admission in the Danish health care system and these discharge diagnoses have documented high validity. The validity of diagnoses of apparently major cardiovascular events that do not lead to subsequent inpatient admission (for example, myocardial infarction coded during emergency room contact without admitting the patient to hospital) have considerably lower validity.

For further details see SAP.

Table 1 Codes for study outcomes

| Variable | Database | Codes |
|---|---|---|
| Hospital Admissions for HF and/or initiation of therapy with loop diuretics | DNPR, prescription registry | Either admission for HF: I500, I501, I502, I503, I508, I509, I110, I130, I132, I420, I426, I427, I428, I429 **OR** initiation of loop diuretic: ATC codes C03C, C03EB |
| Hospital Admission for HF and all-cause death | DNPR, CRS | Either admission for HF: I500, I501, I502, I503, I508, I509, I110, I130, I132, I420, I426, I427, I428, I429 **OR** All-cause death |
| "Expanded MACE": All cause death, non-fatal stroke, non-fatal MI, hospital admission for unstable angina, coronary | DNPR, CRS | Either Admission for MI: I21 **OR** Admission for unstable angina: |

| Variable | Database | Codes |
|---|---|---|
| revascularization, hospital admission for HF | | I200 **OR** nonfatal stroke: I61, I63, I64, **OR** admission for HF:<br>I500, I501, I502, I503, I508, I509, I110, I130, I132, I420, I426, I427, I428, I429,<br>**OR** procedure code CABG:<br>KFNA-KFNE, KFNH20<br>**OR** Procedure code PCI:<br>KFNG, KFNF<br>**OR** All-cause death |

ICD-10 codes for secondary outcomes

| Variable | Database | Codes | Notes |
|---|---|---|---|
| All-cause inpatient hospital admission or emergency room visit | DNPR | Various diagnoses and procedures from all acute hospital contacts | |
| Hospital admission with HF | DNPR | Admission for HF:<br>I500, I501, I502, I503, I508, I509, I110, I130, I132, I420, I426, I427, I428, I429 | |
| All-cause inpatient hospital admission or all-cause death | DNPR, CPR | Various diagnoses and procedures from all inpatient hospital admissions | |

| Variable | Database | Codes | |
|---|---|---|---|
| | | **OR** All-cause death | |
| All-cause death | CPR | All-cause death | |

### 9.3.3 Covariates

For all patients with a first initiation of empagliflozin or GLP1-RA, we will ascertain data on a range of variables potentially associated with the outcomes of interest, including the following:

Included in current analysis as potential confounders: Age, gender, year of inclusion, diabetes duration, number of diabetes drugs used, metformin use, insulin use, diagnoses of retinopathy, neuropathy, or nephropathy, estimated glomerular filtration rate (eGFR), history of ischemic heart disease, cerebrovascular disease, peripheral vascular disease, heart failure (further divided by duration and primary/secondary diagnosis), medical obesity, chronic obstructive pulmonary disease, cancer, use of angiotensin converting-enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs), other antihypertensives, statins, antiplatelet drugs, social and frailty markers, marital status, prescriptions for mental disorders, alcoholism, and number of prior hospital admission days.

Table 2 Codes for other covariates: comorbidities and diabetes complications

| Variable | Database | Codes | Notes |
|---|---|---|---|
| Ischemic heart disease | DNPR | I20-I25, T822A, T823, KFNA, KFNB, KFNC, KFND, KFNE, KFNF, KFNG, KFNH, KFNW, KFLF | Ischemic heart disease diagnosis incl angina or coronary OP |
| Cerebrovascular disease | DNPR | G45, I61, I63-I66, I672, I678-I679, I691, I693-I698, G45, KAAL10, KAAL11 | Atherosclerotic cerebrovascular disease incl thrombolysis/thrombectomy, TCI, intracerebral hemorrhage |
| Peripheral vascular disease | DNPR | I702, I742-I745, I739A, I739B, I739C, E105, E115, E125, E135, E145, KPBE+F+H+N+P+Q, KPBW, KPGH10, KPDE+F+H+N+P+Q, KPDW99, KPDW20, KPEE+F+H+N+P+Q+W, KPFE+H+N+P+Q+W, KPGH20+21+22+23+30+31+40 | Atherosclerotic peripheral vascular disease incl vascular OP or amputation |

| Variable | Database | Codes | Notes |
|---|---|---|---|
| | | +99, KPDU74+82+83+84, KPEU74+82+83+84, KPFU74+82+83+84, KNBQ, KNCQ, KNDQ, KNEQ, KNFQ, KNGQ, KNHQ | |
| Neuropathy | | E104, E114, E144, G590, G632, G598, G603, G628, G629, G632, G638, G990 | |
| Retinopathy | DNPR Diagnosis codes + procedure codes | E103, E113, E143, H340, H341, H342, H280, H334, H450, H360, H540, H541, H544, H25, H268, H269, H430, H431, H438C, H439, H334A, H330, H335, H470<br>KCKC10, KCKC15, KCKD65 | |
| Nephropathy | DNPR Diagnosis codes + | E102, E112, DE142, I120, N083, N06, N17, N18, N19, R809<br>BJFD2 | |
| Creatinine (eGFR) | LABKA | NPU18016, NPU01807, NPU04998, NPU17559, ASS00354, ASS00355, ASS00356 or analysis codes: 110266, 111016, 1311235, 1411235, 1511235, 1511236, 1511237, 1610154, 1610296, 1611807, 1710552, 1710301, 1711807, 1811807, 1817156, 1817428, 18016, 1155, 38927, 4998, 716, 1807, 5224, 38926, 38928 | |
| Chronic pulmonary disease | DNPR | J40-J48, J60-J68, J684, J701, J703, DJ961, J982, J983 | |
| Cancer | DNPR | C00-C99 | |
| Medical obesity | DNPR | E65-E68 | |
| Alcoholism | DNPR | G312, G621, G721, I426, K292, K860, K70, R780, T51, Z714, Z721 | |

| Variable | Database | Codes | Notes |
|---|---|---|---|
| Mental disorders | prescriptions | N05A, N05BA, N05CD, N05CF, N06A | |
| Antiplatelet drugs | prescriptions | B01AC06, N02BA01, B01AC30, B01AC07, B01AC22, B01AC04, B01AC24, B01AC25 | |
| Statins | prescriptions | C10AA, C10BA, C10BX, A10BH51 | |
| Any antihypertensive drugs | prescriptions | C02, C03A, C03B, C03X, C07, C08, C09 | |
| ACE inhibitors | prescriptions | C09A, C09B | |
| ARB | prescriptions | C09C, C09D | |
| Marital status | CRS | | Current marital status (if no current status in CPR, last value carried forward) |

Exhaustive list for lab value data sources and codes can be requested from the corresponding author.

Table 3 Codes for all antihyperglycemic (glucose-lowering) drugs of interest

| Diabetes drugs | ATC codes in database |
|---|---|
| Empagliflozin | A10BX12, A10BK03, A10BD19, A10BD20 |
| Liraglutide | A10BX07, A10BJ02, A10AE56 |
| SGLT2-inhibitor | A10BX09, A10BX11, A10BX12, A10BK, A10BD15, A10BD16, A10BD21, A10BD20, A10BD19, A10BD23, A10BD24, A10BD25 |
| GLP1 receptor agonists | A10BX04, A10BX07, A10BX10, A10BX13, A10BX14, A10BJ, A10AE54, A10AE56 |
| DPP4 inhibitors | A10BH, A10BD07, A10BD12, A10BD08, A10BD09, A10BD10, A10BD11, A10BD13, A10BD18, A10BD19, A10BD21, A10BD22, A10BD24, A10BD25 |
| biguanides | A10BA, A10BD01, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15, A10BD16, A10BD17, A10BD18, A10BD20, A10BD22, A10BD23, A10BD25 |
| sulfonylureas | A10BB, A10BD04, A10BD02, A10BD06, A10BD01, A10BC01 |

| Diabetes drugs | ATC codes in database |
|---|---|
| glitazones | A10BG, A10BD03, A10BD04, A10BD05, A10BD06, A10BD09, A10BD12 |
| alfa-glucosidase inhibitors | A10BF, A10BD17 |
| Insulin and analogues | A10A |
| meglitinides | A10BX02, A10BX03, A10BX08, A10BD14 |

## 9.4 DATA SOURCES

The Danish health care system provides universal coverage to all Danish residents (5.7 million inhabitants. Health care coverage includes visits to general practitioners and specialists, hospital admissions, and outpatient visits. The costs of medicines are partially covered by the Danish health system.

The centralized Civil Registration System in Denmark allows for personal identification of each person in the entire Danish population and for the possibility of linkage to all Danish registers containing civil registration numbers, such as the registers mentioned below.

Data collected in these registers are available for research purposes after following a standard application procedure to the relevant data board. The process requires collaboration with a local university or investigator affiliated with a research institute to access the data; Danish Data Protection Agency approval to handle data; data release by the Danish National Data Board; and, for accessing medical charts, approval of a Patient Safety Board. All applications have to be submitted in Danish.

Denmark's primary health care sector, which includes GPs, specialists, and dentists, generates about 96% of the prescription sales, most of which are reimbursable and are dispensed by community pharmacies. Each dispensing record contains information on the patient, drug, and prescriber. Dispensing records retain the patient's universal personal identifier, allowing for individual-level linkage to all Danish registers and medical databases.

The study will draw on the following Danish population-based registries:

The Civil Registration System: Holds records of central personal registry (CPR)-number, address, marital status, emigration and immigration status, and date of death (if any) of the entire population of Denmark since 1968. This system can be used to link all Danish registries containing CPR-numbers (1).

The Danish National Patient Register: The Danish National Patient Register (DNPR) includes information of all hospitalized patients since 1977 and on outpatient hospital contacts since 1995. The register contains information about the date of admission, discharge, diagnosis codes and surgical procedures. From 1977 to 1993 diagnosis codes were coded with reference to the ICD-8 classification and from 1994 onwards they have been coded according to ICD-10 (2).

The National Database of Reimbursed Prescriptions: Contains complete information on all prescriptions dispensed at community pharmacies in the Danish regions since 1994. Records information about the drug user including civil registration number, age, gender, residence, ATC (Anatomical Therapeutic Chemical) code of the drug, package size, and date of dispensing (3).

The National Laboratory Database: Data from samples which involve laboratory analysis (e.g. blood samples) are compiled in this database. Danish regions were affiliated with the database from 2013. In addition, historical data from some regions have been incorporated.
Data on e.g. creatinine can be extracted from this registry (5).

The National Health Insurance Service Registry: Contains data on all reimbursed primary care encounters and services, such as contacts and services by general practitioners (GP), privately practicing specialist physicians, psychologists, physiotherapists, dentists, podiatrists, etc.

The Danish Diagnosis-Related Group (DRG) and Danish Ambulatory Grouping System (DAGS): contains costs for all hospital contacts and procedures recorded in The Danish National Patient Register (see above); updated until 2018.

## 9.5 STUDY SIZE

In general, the study size will be driven by the uptake of empagliflozin following approval and launch of empagliflozin for the treatment of T2D to improve glycaemic control in adults in Denmark in 2014. In 2019, according to www.medstat.dk there were 23,350 users of empagliflozin in Denmark,

In 2019, there were 41,715 users of GLP-1 receptor agonists in Denmark (9). This may yield an estimated at least 50,000 GLP-1 RA users during 2014-2020 for comparison making statistical power a minor concern when including 2020 data in the final analysis.

We thus estimate that at least 40,000 person-years of empagliflozin exposure and 60,000 person-years of liraglutide exposure can be included in our study up to the end of 2020.

## 9.6 DATA MANAGEMENT

The [redacted] at [redacted] is a large academic department, with more than 15 years' experience conducting data management and epidemiologic research based on Danish registry data. This includes several successfully fulfilled calls from the EMA, specifically on utilization and safety of antidiabetic agents using Danish registry data. The department has a cadre of 25 statisticians at Master or PhD level, one of whom will be assigned to this project for its duration.
Standard security processes at [redacted] will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.
All conversion of the original data to analysis variables will be performed using SAS software version 9.4 (SAS Institute, Inc., Cary, North Carolina).

## 9.7 DATA ANALYSIS

We will provide two approaches in our study across the two exposure groups: an on-treatment (OT) exposure definition, and an intention-to-treat (ITT) exposure definition (see section 9.1 for details).

Decisions to start a specific glucose-lowering drug are influenced by demographic, medical, and clinical factors, and those same factors might be associated with the outcomes of interest. For balanced comparison of the two treatment groups, we plan to conduct propensity score (PS) balancing of potential confounders (see section 9.3, covariates) across the two treatment groups. Covariate balance will be assessed by checking standardized differences (SD) between the groups; a covariate being considered well balanced if the SD is below 0.1.

The propensity score is the predicted probability of being assigned to a particular treatment conditional on a set of observed covariates. Because a propensity score model predicts not the probability of experiencing the (relatively rare) outcome but the probability of the (frequent) exposure i.e. being treated with empagliflozin or GLP1-RA in this study, more of our potential confounding covariates may be used in the model than in a conventional multivariable regression model. As recently discussed (Kahlert et al: Control of confounding in the analysis phase. Clin Epidemiol 2017), in the majority of studies that have used both multivariable analysis and propensity score methods, there were no important differences in the results. Propensity score methods may be more robust in situations with rare outcomes and common exposures than traditional multivariable analysis, as expected in our proposed study. However, just as with multivariable analysis, propensity score methods do not protect against unknown, unmeasured and residual confounding when comparing GLP1-RA and empagliflozin initiators. Moreover, propensity score methods may not in some settings estimate treatment effects in the entire population of real-world treated individuals but in a trimmed subset of the data, limiting sample size and in some cases hampering the feasibility and interpretability of the results obtained by the propensity score method. Therefore, our approach will be to examine and learn about the data available in our dataset, apply stratified analyses and investigate available confounders and sample size, and then seek to apply the methods.
Given that 1) We aim to measure the average treatment effect at the population level; 2) We wanted to avoid excluding patients, to reduce the risk of a non-representative sample; and 3) The number of patients in our two treatment groups will likely differ little, the Inverse Probability Treatment Weighting approach (IPTW) may be a feasible approach

Cumulative incidence function curves adjusted for competing risk will be constructed to depict the cumulative incidence over time of each of the outcomes under study, comparing empagliflozin and GLP1-RA initiators.

We will use Cox regression analyses to compute crude and adjusted hazard ratios (HRs) with 95% CIs to examine the association between empagliflozin versus GLP1-RA initiation and study outcomes. For each of the primary outcomes (primary objective) and secondary outcomes (secondary objective) of interest, estimation of adjusted use HRs with 95% CIs will be considered the main analysis of interest.

The selection of variables to be included in the Cox regression model will be based on evidence from previous literature, covariate data availability, examination of exposure group differences in the distribution of each covariate, and the association of covariates with the outcomes of interest. The current list of potential confounders for the Cox regression model is included in section 9.3. The variable list may be subject to changes in which case these will be included in an amendment process and will be reflected in the SAP.

*Stratified analyses*

A number of stratified analyses will be performed to assess effect measure modification and possible residual confounding.

Relative risk estimates will be calculated, stratified by strata of sex, age (<65, >=65 years), presence or absence of cardiovascular disease at baseline (ischemic heart disease, HF, cerebrovascular disease, or peripheral vascular disease), current insulin use, current metformin use, and calendar periods before and after publication of the two major CVOTs (Jan 2015 – June 2016, July 2016 – Dec 2018).

[redacted]

## 9.8 QUALITY CONTROL

Quality control and management will follow the routines of [redacted].

## 9.9 LIMITATIONS OF THE RESEARCH METHODS

Several clinical epidemiological studies involving linkage between the prescription and laboratory database and the other Danish population-based data sources have been published in major international peer reviewed journals, thus the quality of the data sources is well established within the epidemiologic field (5).

Selection bias: These studies will use unique population-based databases and include all patients with known medically treated type 2 diabetes in the regions. As there is virtually no loss to follow-up, the risk of selection bias in the cohort studies will be negligible.

Information bias: All studies are based on administrative coding and are thus dependent on validity and reliability of registry data. For diabetes, the National Diabetes Register has documented sensitivity and positive predictive value (PPV) above 85% when using prescription and hospital contact data (3). The PPVs for important comorbidities are also documented high in the patient registry. Filled prescriptions are only a marker of actual drug consumption and there is a possibility of non-compliance to treatment. This will bias the possible effects of the examined drugs and any differences in drug effects towards the null.

Confounding: By controlling for confounding during the analysis phase and by undertaking stratified analysis, we will be able to reduce the confounding effect of a range of measurable variables as explained above. Unmeasured or unknown confounders may still affect our relative risk estimates in the outcome analyses, and misclassification of data on confounders may lead to some residual confounding. In particular, in this study there will be no access to journal data from primary care journals, thus vital clinical data for e.g. smoking habits, blood pressure and weight in most patients are missing. This might hamper effectiveness comparisons between different treatment regimens. We will do an assessment of the possible impact of unmeasured confounding as decribed above.
Considering drug exposure, our on-treatment (i.e., terminating drug exposure upon discontinuation) may be prone to bias if the discontinuation of a study drug (empagliflozin or GLP1-RA) predicts future cardiovascular outcomes or death (informative censoring)(27) We will therefore evaluate the temporal distribution of outcome occurrence shortly after drug discontinuation, to assess the presence of informative censoring. Our intention-to-treat

approach (i.e., carrying forward the initial exposure status and disregarding changes in treatment status over time) is not affected by informative censoring bias in the same way, but may on the other hand be biased through exposure misclassification that increases with longer follow-up periods and is open to potential differential loss to follow-up (27). We will therefore consider results from both analyses carefully in evaluating the clinical effects of empagliflozin and GLP1-RA, in light of the strengths and limitations inherent in each approach.

# 10. PROTECTION OF HUMAN SUBJECTS

According to Danish law, individual informed consent, or permission from ethical committee, is not required for observational registry-based studies without patient contact. The project has been approved by the Danish Data Protection Agency (Record number 2014-54-0922 KEA-2015-4).

# 11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable based on secondary use of data without any potential that any employee of BI or agent working on behalf of BI access individually identifiable patient data.

# 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The [redacted] reserves the right to submit the results from any of the study analyses for publication and commits that at least the final results will be published. Any publications will follow guidelines, including those for authorship, established by the International Committee of Medical Journal Editors. When reporting results of this study, the appropriate STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist will be followed.

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# ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

# ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMEA/540136/2009
Doc.Ref. EMA/540136/2009

**ENCePP Checklist for Study Protocols (Revision 3)**

Adopted by the ENCePP Steering Group on 01/07/2016

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 as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

**Study title:**

Cardiovascular outcomes, and mortality in Danish patients with type 2 diabetes who initiate empagliflozin versus GLP1-RA: A Danish nationwide comparative effectiveness study - EMPLACE™

**Study reference number:**

http://website.encepp.eu/encepp/viewResource.htm?id=37726

| **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 Study progress report(s) | ☐ | ☐ | ☒ | |
| 1.1.4 Interim progress report(s) | ☒ | ☐ | ☐ | 6 |
| 1.1.5 Registration in the EU PAS Register | ☒ | ☐ | ☐ | 6 |
| 1.1.6 Final report of study results | ☒ | ☐ | ☐ | 6 |

Comments:

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| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | | | | |
| 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) | ☒ | ☐ | ☐ | 9.2.1 |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | |
| 2.1.5 If applicable, that there is no a priori hypothesis? | ☐ | ☐ | ☒ | |

Comments:

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1 Date from wh ch informat on on the first study is first recorded in the study data set or, in the case of secondary use of data, the date from wh ch data extract on starts

2 Date from which the analytical data set is completely available

| **Section 3: Study design** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 3.1 | Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative 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. incidence rate, absolute risk) | ☒ | ☐ | ☐ | 9.1 |
| 3.4 | Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year) | ☒ | ☐ | ☐ | 9.1 |
| 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) | ☒ | ☐ | ☐ | 11 |

Comments:

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| **Section 4: Source and study populations** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 4.1 | Is the source population described? | ☒ | ☐ | ☐ | 9.2.1 |
| 4.2 | Is the planned study population defined in terms of: | | | | |
| | 4.2.1 Study time period? | ☒ | ☐ | ☐ | 9.2.2 |
| | 4.2.2 Age and sex? | ☒ | ☐ | ☐ | 9.2.1 |
| | 4.2.3 Country of origin? | ☒ | ☐ | ☐ | 9.2.1 |
| | 4.2.4 Disease/indication? | ☒ | ☐ | ☐ | 9.2.1 |
| | 4.2.5 Duration of follow-up? | ☒ | ☐ | ☐ | 9.2.8 |
| 4.3 | Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 9.2.6, 9.2.7 |

Comments:

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| **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) | ☒ | ☐ | ☐ | 9.3.1 |

| **Section 5: Exposure definition and measurement** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 5.3 | Is exposure classified according to time windows? (e.g. current user, former user, non-use) | ☒ | ☐ | ☐ | 9.3.1 |
| 5.4 | Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☐ | ☒ | ☐ | |

Comments:

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| **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 |
| 6.2 | Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | 9.3.2 |
| 6.3 | Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study) | ☒ | ☐ | ☐ | 9.3.2 |
| 6.4 | Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management) | ☐ | ☒ | ☐ | |

Comments:

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| **Section 7: Bias** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 7.1 | Does the protocol describe how confounding will be addressed in the study? | ☒ | ☐ | ☐ | 9.9 |
| | 7.1.1. Does the protocol address confounding by indication if applicable? | ☒ | ☐ | ☐ | 9.9 |
| 7.2 | Does the protocol address: | | | | |
| | 7.2.1. Selection biases (e.g. healthy user bias) | ☒ | ☐ | ☐ | 9.9 |
| | 7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias) | ☒ | ☐ | ☐ | 9.9 |
| 7.3 | Does the protocol address the validity of the study covariates? | ☒ | ☐ | ☐ | 9.3.3 |

Comments:

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| **Section 8: Effect modification** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect) | ☒ | ☐ | ☐ | 9.9 |

Comments:

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| **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 |
| 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 |
| 9.1.3 Covariates? | ☒ | ☐ | ☐ | 9.4 |
| 9.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☐ | ☐ | ☐ | 9.4 |
| 9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event) | ☐ | ☐ | ☐ | 9.4 |
| 9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, comorbidity, comedications, lifestyle) | ☐ | ☐ | ☐ | 9.4 |
| 9.3 Is a coding system described for: | | | | |
| 9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☒ | ☐ | ☐ | 9.4 |
| 9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA)) | ☒ | ☐ | ☐ | 9.4 |
| 9.3.3 Covariates? | ☒ | ☐ | ☐ | 9.4 |
| 9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other) | ☒ | ☐ | ☐ | 9.4 |

Comments:

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| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.1 Is the choice of statistical techniques described? | ☒ | ☐ | ☐ | 9.7 |
| 10.2 Are descriptive analyses included? | ☐ | ☒ | ☐ | |
| 10.3 Are stratified analyses included? | ☒ | ☐ | ☐ | 9.7 |
| 10.4 Does the plan describe methods for adjusting for confounding? | ☒ | ☐ | ☐ | 9.7, 9.9 |
| 10.5 Does the plan describe methods for handling missing data? | ☐ | ☒ | ☐ | |
| 10.6 Is sample size and/or statistical power estimated? | ☒ | ☐ | ☐ | 9.5 |

Comments:

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| **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) | ☒ | ☐ | ☐ | 9.8 |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 9.8 |
| 11.3 Is there a system in place for independent review of study results? | ☐ | ☒ | ☐ | |

Comments:

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| **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? | ☒ | ☐ | ☐ | 9.9 |
| 12.1.2 Information bias? | ☒ | ☐ | ☐ | 9.9 |
| 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) | ☒ | ☐ | ☐ | 9.9 |
| 12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment) | ☐ | ☒ | ☐ | |

Comments:

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| **Section 13: Ethical 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? | ☐ | ☒ | ☐ | |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 10 |

Comments:

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| **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:

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| **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)? | ☒ | ☐ | ☐ | 12 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 12 |

Comments:

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

Date: 22 Oct 2020

Signature:

# ANNEX 3. ADDITIONAL INFORMATION

Not applicable