Non-Interventional Study Protocol Amendment

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Characteristics and cardiovascular and mortality outcomes in patients with type 2 diabetes mellitus initiating treatment with sodium-glucose co-transporter-2 inhibitors and other diabetic medications

This protocol amendment concerns Step 2 of this study which will analyze the risk of cardiovascular (CV) outcomes and all-cause mortality in patients with type 2 diabetes mellitus (T2DM) who initiate use or treatment with sodium-glucose co-transporter-2 (SGLT-2) inhibitors compared to patients initiating other diabetes medications (other glucose lowering drugs). The study will use observational data from databases in US (Humedica, MarketScan), UK (CPRD, THIN), the Nordic countries (Sweden, Denmark and Norway), Germany (DPV) and Canada.

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ATC	Anatomical Therapeutical Chemical Classification system
CPRD	Clinical Practice Research Datalink
CV	Cardiovascular
CVD	Cardiovascular disease
DPP-4i	Dipeptidyl peptidase-4 inhibitors
GLP-1ra	Glucagon-like peptide-1 receptor agonists
HF	Heart failure
ICD	International Classification of Diseases
MI	Myocardial infarction
RCT	Randomized Clinical Trial
SGLT-2i	Sodium glucose cotransporter-2 inhibitor
SOC	Standard of care
SU	Sulfonylureas
T2DM	Type 2 diabetes mellitus
THIN	The Health Improvement Network
UK	United Kingdom
US	United States

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PROTOCOL SYNOPSIS

This protocol amendment concerns Step 2 of a study which will analyze the risk of cardiovascular (CV) outcomes and all-cause mortality in patients with type 2 diabetes mellitus (T2DM) who initiate use or treatment with sodium-glucose co-transporter-2 (SGLT-2) inhibitors compared to patients initiating other diabetes medications (other standard of care treatments). The study will use observational data from databases in US (Humedica, MarketScan), UK (CPRD, THIN), and the Nordic countries (Sweden, Denmark and Norway), Germany (DPV) and Canada (MCHP).

Background/Rationale: In September 2015 the EMPA-REG trial presented data on positive effects of empagliflozin, a SGLT-2 inhibitor on CV outcomes. This has created a need for data on how this class of medicines affect CV event rates when used in clinical practice. An observational study can never replicate a randomized controlled trial (RCT) since neither placebo treatment nor randomisation is part of clinical practice. An observational study will instead use an active comparator group. To provide a good comparison, the treatment arms should have ideally exchangeable treatment alternatives, similar patient characteristics and baseline risk of the outcome. For medication classes recently introduced on the market, such as the SGLT-2 inhibitors, it may be difficult to find a suitable comparator and the number of patients exposed and length of exposure may be limited. Therefore this study has two steps where step 2 is described in this amendment. Step 1 assesses the number of patients initiating use with this class of medicines and their length of follow up as well as describes characteristics of new users of SGLT-2i and potential comparator groups. Step 1 is now completed and shows that a suitable comparator group can be identified and that there is sufficient statistical power to conduct a comparative analysis of the outcomes of interest (Step 2). This step is described in this amendment.

Objectives and Hypotheses: The primary aim of this study is to compare the risk for hospitalization for heart failure, inpatients with T2DM who are new users of a SGLT-2 inhibitor versus an active comparison group including patients with T2DM who are new users of other glucose lowering drugs (GLD). A secondary aim is to compare all-cause mortality using similar methods. Exploratory aims are to estimate the incidence of acute myocardial infarction and atrial fibrillation in both treatment groups.

Methods:

Study design: Cohort study (Section 3.1)

Data Source(s): In the UK CPRD, THIN; in the US Humedica, MarketScan; in Sweden the DAISY database; in Norway the DAPHNE database and in Denmark the DAFFODIL database; in Germany ("Diabetes Patientenverlaufsdokumentation" [DPV]) and Manitoba Centre for Health Care Policy (MCHP) in Canada (Section 3.1.1)

Study Population: New users of SGLT-2i and other GLD respectively (Section3.2)

Exposure(s): SGLT-2i and other GLD (Section 4.1)

Outcome(s): Hospitalization for heart failure, all-cause mortality (only possible in UK and the Nordic countries), acute myocardial infarction and atrial fibrillation respectively. (Section 4.2)

Sample Size Estimations: The primary endpoint will be hospitalization for heart failure. A risk reduction in this endpoint of 20% for the SGLT-2i group compared to the control group will be considered clinically meaningful. For 85% power to detect a risk reduction of 20% with a two-sided alpha level of 0.05, and up to 1:3 treatment allocation of SGLT-2i to the comparator arm, a total of 970 events will be needed across both treatment groups and all databases after the matched SGLT-2i and control groups have been created. This calculation assumes the background rate of hospitalization for heart failure in the standard of care group is 0.625 events per 100 person-years. For 1:3 treatment allocation, approximately 40,842 person-years will be needed in the SGLT-2i group and 122,526 person-years will be needed in the control group. However, the key driver for the power and the analysis is the number of events. The sample size is merely an approximation of how many person-years might produce the required number of events based on the assumed event rates. Also, the ratio of SGLT-2i: control matching may vary across the databases but as long as a total of 970 events are achieved, the analysis will be sufficiently powered.

The background rate of 0.625 events per 100 person-years is relevant for US, UK and Germany based on literature and empirical rates from the databases included in the study. Based on Swedish data, a substantially higher rate of 1.58 events per 100 person years has been observed. This difference in rates could be due to the age distribution and other factors including case ascertainment and baseline cardiovascular risk.

As there may not be enough statistical power for a standalone analysis in any of the individual country databases, a meta-analysis approach will be used to conduct the treatment comparison by pooling the hazard ratio estimates from all of the databases assuming that a total of 970 events have been observed. The higher rate of 1.58 events per 100 person years may apply in Sweden and the other Nordic countries. This higher event rate allows for the possibility of a sufficiently powered analysis in the Nordics alone. If 970 events have been observed in the Nordics, then a separate analysis will be submitted for the Nordics database. Assuming 1:3 matching, approximately 16,019 person-years will be needed in the SGLT-2i group and 48,054 person-years will be needed in the control group to obtain the target of 970 events.

Statistical Analysis: The primary objective of step 2 is to compare the incidence of heart failure hospitalization between new users of SGLT-2 inhibitors and the comparator arm using a hazard ratio (relative risk) and corresponding 95% confidence interval. The analysis will be performed using the Cox proportional hazards model or some other

appropriate method. The secondary endpoint of interest, (all-cause mortality), will also be compared between the SGLT-2i group and comparator arm using a similar statistical method. In addition, the exploratory outcomes, the baseline characteristics and other clinical parameters for each treatment group will be summarized descriptively. Matching by propensity scores will be used to balance the potential confounding covariates between the SGLT-2i group and the reference group to ensure that the two groups are as similar as possible at baseline. This is described in Section 5. To achieve sufficient power, a meta-analysis based on the DerSimonian-Laird random effects model will be applied to integrate the point estimates from each of the individual database analyses and calculate an overall weighted estimate and corresponding 95% CI [6]. A standalone analysis may be implemented in the Nordics database assuming that a total of 970 events have been observed.

AMENDMENT HISTORY

Date	Brief description of change	Administrative Change / Amendment / New Protocol Version.
April 12, 2016	Amendment describing the analyses in Step 2	Amendment
Protocol revised August 18	Inclusion of additional countries (Norway, Denmark, Germany and Canada) and incorporating suggestions from the external Publication Steering Committee	New Amendment Version
Protocol revised October 26	Including suggestions from the external Publication Steering Committee. Adjusted based on data availability and estimates of background rates.	New Amended Version
Revised protocol November 22	Including suggestions from MARC and GPT review and updates from countries and databases.	New Amended Version

MILESTONES

Date	Milestone
Q4 2015	Development of Study Concept Sheet
Q4 2015	Final Protocol
November 17 2015	Development of Study Concept Sheet
December 16 2015	Internal scientific review of protocol
December 31 2015	Approval of protocol
	Database/EC/IRB approvals
June, 2016	– CPRD+THIN (ISAC and SRC approval Step 1)
	Core data sets set up
May 4, 2016	– THIN
February 28, 2016	– Humedica
April 30, 2016	– MarketScan
February 15, 2016	– Sweden
	Final results tables step 1
September, 2016	– CPRD+THIN
July 31, 2016	– Humedica
March 31, 2016	– MarketScan
November, 2016	– Update Sweden
November, 2016	– Denmark
November, 2016	– Norway
September 15, 2016	– Germany
	– Canada
	Abstract and publication step 1
October 15	– Abstract draft
November	– Abstract submitted
January 2017	– Manuscript first draft
February 2017	– Manuscript submitted
	Step 2 results comparative analysis
January, 2017	CPRD/THIN (ISAC/SRC subm. step 2 Sep16. Awaiting free text. ISAC approval pending)
July 31, 2016	Humedica
May 13, 2016	MarketScan
December, 2015	Sweden
November 1, 2016	Germany
February, 2017	Canada
	Step 2 combined comparative analysis of risk
December 10, 2016	All databases combined in meta-analysis
December 15, 2016	Abstract draft
December 20, 2016	Abstract submitted

1. BACKGROUND AND RATIONALE

1.1 Rationale for the amendment

In September 2015 the EMPA-REG trial presented data on positive effects of empagliflozin, a SGLT-2 inhibitor on CV outcomes. [1] This has created a need for data on how this class of medicines affect CV event rates when used in clinical practice. An observational study cannot replicate the design and results of a placebo-controlled randomized clinical trial since neither randomisation nor placebo treatment are part of clinical practice. An observational study will need to compare against an active comparator and disease severity as well as prescriber preferences influence the choice of treatment. This may introduce differences in patient characteristics associated with the treatment choice as well as the outcome and is referred to as confounding by indication or channeling bias. The choice of comparator in observational studies requires careful selection and consideration in order to find a comparator with as similar patient characteristics regarding demographics and disease progression as possible. Patients with T2DM include a large span of disease severity which is important to account for; one marker of this is insulin use. As seen in the EMPA-REG population insulin use is common in T2DM patients with established CVD [1]. The SGLT-2i class is relatively recently introduced on the market in both Europe and the US, introduced in November 2012 and March 2013, respectively. Thus both the number of patients exposed to this class of drugs and their follow up time on the medicines are limited.

This protocol amendment concerns the second step (Step 2) of the study. The rationale for conducting the first step (step 1) descriptive study was to gain more insight into the patient characteristics of patients at high baseline CV risk initiating use with SGLT-2i, and specifically dapagliflozin, and four potential comparator groups (DPP-4i, SU, GLP-1ra and a group containing all other glucose lowering drugs (GLD) except SGLT-2 inhibitors) in different countries (United States (US), United Kingdom (UK), Sweden, Denmark, Norway, Germany and Canada). Further, since SGLT-2i were recently marketed little is known on the patient characteristics in general of users of these medications in comparison with patient characteristics of users of other medication classes. It is likely that they differ since SGLT-2i have primarily been recommended as third line treatment in many countries. Previous studies have reported some differences in patient characteristics between new users of DPP-4 inhibitors compared to SU concerning age, diabetes duration and concomitant medication use [2-5]. More differences have been reported between SU users and GLP-1ra users in age, treatment duration and concomitant medications used [3]. This stresses the importance to assess several potential comparator groups to find a suitable comparison group.

The results from the first part of this study (step 1) are descriptive and inform whether it will be feasible to conduct a comparative effectiveness study, assessing the effects of SGLT-2i versus an active comparator, on CV and mortality outcomes (step 2). This study will require adequate power and comparator as well as relevant data for cohort selection and outcomes and to perform required statistical modeling to address channeling bias.

A comparative effectiveness study could fill a current knowledge gap for SGLT-2i as a class in light of the result from the first SGLT-2 inhibitor CV outcomes trial [1].

The study design of the step 2 i.e. this protocol amendment is presented here.

2. OBJECTIVES AND HYPOTHESES

2.1 Primary Objective(s) & Hypothesis(es)

This study has been divided in two steps where step 1 has assessed the study population length and follow up as well as comparability between SGLT-2i users and users of other diabetes medication groups. The objectives of step 1 are described in the full protocol (D1690R00015). This amendment concerns step 2 which is a comparative analysis of the risk for CV events between SGLT-2i users and a group of active comparators.

Step 2 has one primary, one secondary and two exploratory objectives and will only be conducted given that a comparative analysis is feasible based on the results from step 1. Feasibility was determined by the following requirements a) the study population has enough length of follow up, required variables of interest, and size to have sufficient power to assess the outcome of interest according to the power calculations presented in Section 5.3 and b) a suitable comparator group. Suitability of comparator groups was assessed based on the propensity score matching by applying normal requirements to assess sufficient match between different groups. This process will be outlined in more detail in the statistical analysis plan (SAP). Step 1 also informed whether analysis needed to be done on SGLT-2i class level or dapagliflozin separately applying the above-mentioned criteria. As step 2 is considered feasible based on the criteria, this protocol amendment outlines the analysis including the specifics about the treatment group, comparator group, and primary outcome, for this step. The primary, secondary and explorative objectives of the study amendment (step 2) are:

<u>Primary objective</u>

To compare the risk for hospitalization for heart failure between patients with T2DM who are new users of SGLT-2 inhibitors as a class versus an active comparison group including patients with T2DM who are new users of other GLD.

<u>Secondary objective</u>

To compare all-cause mortality between patients with T2DM who are new users of SGLT-2 inhibitors as a class versus an active comparison group including patients with T2DM who are new users of other GLD. Due to data availability this objective can only be addressed in UK and the Nordic countries.

<u>Exploratory objectives</u>

To estimate the incidence of acute myocardial infarction and atrial fibrillation respectively in new users of SGLT2 inhibitors and of other GLD.

3. METHODOLOGY

3.1 Study Design – General Aspects

This is a cohort study of patients with T2DM who are new users of SGLT-2 inhibitors and other GLD, respectively, in the US, UK, Sweden, Denmark, Norway, Germany and Canada. Additional countries contributing with corresponding data fulfilling the

requirements for the objectives of the study as described in the main protocol (D1690R00015) may be added in a second phase of this study.

The study period will range from launch of the first SGLT-2i in each of the countries (November 2012 for Nordics, Germany and UK, March 2013 for US, and January 2015 in Canada) and end at latest available data in each data source.

A new user of SGLT-2i, or another diabetes medication, is defined as an individual receiving a prescription or filling a prescription of the mentioned diabetes medication classes with no issued/dispensed prescriptions of that medicine class during the preceding year.

The date of the first issued /filled prescription of the SGLT-2i and other GLD (index medication group) during the study period will be denoted the *index date*. For the other GLD group consisting of all other diabetes medications except SGLT-2 inhibitors the first initiation of a new diabetes medication class will be the index date for those initiating only one treatment episode in this group during the study period. For patients in this group initiating two or more diabetes medication classes during the study period, one of the episodes will be randomly selected and the first day of that episode will be the index date for that patient. Patients will be followed from index date (excluding) to the earliest of end of use of the index medication group, migration/leaving the practice/leaving the database, last date of data collection, death date or date of outcome. The availability of some of this information differs between databases.

Baseline characteristics including demographic and clinical characteristics will be captured for patients before the index date (including).

3.1.1 Data Source(s)

Several observational data sources from different countries will be included in this study to obtain a large enough population. These databases include MarketScan and Humedica databases from the United States, the DAISY database from Sweden, the DAPHNE database from Norway, the DAFFODIL database from Denmark and from the United Kingdom the Clinical Practice Research Datalink (CPRD), The Health Improvement Network (THIN), the "Diabetes Patienten Verlaufsdokumentation" (DPV) register from Germany and Manitoba Centre for Health Policy (MCHP) in Canada. AstraZeneca has access to several of these databases in-house. The databases are described more in detail in the full protocol (D1690R00015).

The contents and coverage of different variables vary between databases, therefore a set of core variables for both patient characteristics and CV events and mortality will be developed which will be described in all databases. In addition, specific variables of interest including baseline characteristics and CV events and mortality available in a limited number of the databases will also be described where appropriate.

Based on the results from the initial study (Step 1), meta-analyses for hospitalization for heart failure and all-cause mortality are feasible when including exposure-time data from all countries. However, there may not be enough subjects and person-years of exposure in the databases for each country to do standalone analyses for either endpoint. Therefore,

the analyses for these countries will be incorporated into a meta-analysis, the details of which are described below (Section 5.1).

3.2 Study Population

New users will be defined as individuals with T2DM either receiving or filling a prescription of a SGLT-2i or other GLD during the study period. The other GLD comparator group will include all diabetes medicines, allowing combinations and monotherapy use with the exception of SGLT-2i. Comparators will be matched on baseline characteristics for up to a 1:3 ratio for each SGLT-2i user.

The class SGLT-2i include dapagliflozin, canagliflozin and empagliflozin. Individuals with a previous issued/filled prescription of that medicine class during the preceding year (i.e. 365 before the index date) are not regarded as new users.

The date of the first issued /filled prescription of the SGLT-2i and other GLD classes (index medication group) during the study period will be denoted the *index date*. For the group consisting of all other diabetes medications except SGLT-2 inhibitors the first initiation of a new diabetes medication class will be the index date for those in this group initiating only one treatment episode during the study period. For patients in this group initiating two or more diabetes medication classes during the study period, one of the episodes will be randomly selected and the first day of that episode will be the index date for that patient.

A history of CV event is defined as a diagnosis of MI, unstable angina, stroke, heart failure, TIA, coronary revascularization (CABG or PCI) or occlusive peripheral artery disease before the index date. ICD-codes for these are provided in Table 8.1 in section 8 in the full protocol (D1690R00015). Other CV risk factors that also will be assessed but not included in the definition of history of CV events include obesity, dyslipidemias (hypercholesterolemia), hypertension, end stage renal disease and low socioeconomic status. These will be assessed where possible.

3.3 Inclusion Criteria

Inclusion criteria are:

- New user receiving or dispensed prescription of SGLT-2i medication or other GLD, oral as well as injectable, including fixed-dose combination (FDC) products containing these medication groups
- T2DM diagnosis on or prior to the index date defined by ICD9 codes 250.X0, 250.X2 or ICD10 codes E11 and 024.1. Read codes for T2DM are presented in the full protocol (D1690R00015) Table 8.2 in section 8.
- $\geq$ 18 years old at index date
- > 1 year data history in the database prior to the index date

3.4 Exclusion Criteria

Exclusion criteria are:

- Patients with a T1DM diagnosis (ICD9 codes 250.x1, 250.X3 or ICD 10 codes E10 and O24.0, read codes for T1DM are presented in the full protocol (D1690R00015) Table 8.2) at any time

- Patients with gestational diabetes (ICD9 codes648.8; ICD10: O24.4; read codes L180811 and L180900) within 1 year before index date

3.5 Participant Follow-up

Participants will be followed from the index date (excluding) until end of use of the index treatment or migration/leaving the practice/leaving the database, last date of data collection, death date (Sweden, Denmark, Norway, UK) or date of outcome.

4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

4.1 Exposures

The exposure of interest is use of SGLT-2 inhibitors (dapagliflozin, canagliflozin and empagliflozin) or other GFLD including all diabetes medications except initiation of SGLT-2 inhibitors. An individual will be defined as a user on the index therapy for the duration of subsequent prescriptions. A 100 % of previous number of days' supply will be added after the last day of supply. If there is no refill within this period the patient is censored at the last day of the grace period. An individual will only be included if he or she is a new user of one of the mentioned medicine groups. Insulin use in the three months preceding index date will be assessed and descriptions of characteristics will be conducted by insulin use before index date.

An individual will be considered exposed to the medication of interest from the index date and until the last day with medication available (either last day of the last filled prescription (Sweden, Norway, Denmark, Germany, Humedica, MarketScan, Canada's MCHP) or last day of the last issued prescription (CPRD and THIN) plus a grace period of the number of day's supply contained in the last filled or issued prescription.

The SGLT-2i class is defined as the medications dapagliflozin (ATC code A10BX09, A10BD15), canagliflozin (A10BX11, A10BD16) and empagliflozin (A10BX12, A10BD19). DPP-4i includes all available medicines in the ATC category A10BH and the substances A10BD07,08,10,11,13,18 (combinations with metformin). The group other diabetes medications include all diabetes medications in A10A and A10B except SGLT-2 inhibitors. Brand names used in the US of the medication groups are outlined in Table 8.3 in section 8 appendix in the full protocol (D1690R00015).

4.2 Outcomes

Four outcomes are studied in step 2. Firstly, hospitalization for heart failure (ICD-9 code 428.xx, ICD-10 code I50) will be studied and secondly all-cause mortality will be assessed (only in UK (CPRD and THIN) and the Nordic countries). Read codes will be listed separately. Acute myocardial infarction (ICD 9 code 410 and ICD 10 code I21) and atrial fibrillation (ICD 9 code 427.3 and ICD 10 code I48) will be assessed descriptively.

4.3 Other Variables and Covariates

Covariates will be measured to describe baseline characteristics of the study population. A set of core covariates will be determined where data is available in all databases and is described in the full protocol (D1690R00015). Additional covariates will be described

where available in specific databases. Baseline covariates will be measured prior to the index date (including) (age will be on index date) and by clinical coding from either primary or secondary care records. Therapies at baseline will be assessed in the twelve months before and on the index date except for diabetes medication at baseline. Diabetes medication at baseline will be assessed in the twelve months before the index date (excluding).

5. STATISTICAL ANALYSIS PLAN

5.1 Statistical Methods – General Aspects

The incidence rates for heart failure hospitalization will be compared between new initiators of the SGLT-2 inhibitors and the comparison arm (new initiators of other GLD) using hazard ratios (or some other appropriate measure) and corresponding 95% confidence intervals. In this ratio, SGLT-2i as a class will be considered the test treatment. All-cause mortality will also be compared between the SGLT-2 group and control group (other GLD) using similar statistical methods. The treatment comparisons for both these endpoints will be performed separately for each individual country and the point estimates will then be pooled together for an overall weighted summary estimate using the DerSimonian-Laird meta-analysis approach [6].

5.1.1 Primary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. descriptive statistics, hazard ratios, incidence rates, test/retest reliability)

Propensity score
To assess the possible imbalances in baseline covariates between treatment groups which may result in confounding, a propensity score approach will be utilized. Propensity scores will be calculated after the relevant inclusion/exclusion criteria are applied. The propensity score for each subject is the predicted probability of being assigned to a particular treatment conditional on a set of observed covariates. All observed variables that may affect treatment assignment or the outcome of interest will the included in the propensity score [7]. The variables to be considered for the estimation of the propensity score include age at index date, gender, duration of lookback time, indicator variable for time from start of the study period to the index date, indicator variable for whether the index medication was an add-on or switch from the previous medication, medical conditions, cardiovascular risk factors, indicators of diabetes severity (including duration of diabetes), short or long term insulin use, other concomitant medications, lifestyle/ socioeconomic status indicators, and indicators of health care utilization. Patients will be grouped into categories such that patients within a certain category should have similar propensity scores. To determine whether there is balance in key covariates between treatment groups, the covariate distribution between the treatment groups will be compared by creating a table with the frequency distribution of each key covariate by index drug use before and after propensity score matching. For matching the following method is proposed: nearest neighbor caliper width of 0.25 multiplied by the standard deviation of the propensity score distribution [7].

Descriptive analyses

Once the propensity scoring has been applied and the matched groups of SGLT-2i and control subjects have been created, certain baseline and disease characteristics (covariates) will be described by treatment group. These baseline characteristics can include age, gender, duration of diabetes, HbA1c, geographic region of residence, medical conditions, cardiovascular risk factors, concomitant medications, and certain lifestyle/ health care utilization variables, as data permit. These lifestyle/ health care utilization variables can include body mass index, smoking history, alcohol use, socioeconomic status, race/ethnicity, number of outpatient visits, number of hospitalizations, number of emergency department visits, and number of specialty care visits. These characteristics will be assessed for all patients and for patients at high baseline CV risk, respectively.

Categorical variables will be described by frequencies and percentages. Continuous and count variables will be described using mean (± standard deviation [SD], 95% confidence intervals (95%CI), median (quartiles), and minimum and maximum values. The proportion of patients falling above/below certain weight/BMI and HbA1c thresholds will be derived.

The incidence of acute myocardial infarction and atrial fibrillation respectively will be estimated by country/database and by treatment group.

Comparative analyses

Incidence analyses of hospitalization for heart failure and all-cause mortality will be conducted by treatment group. Only the first episode of the event will be included in the incidence analyses (however, the subsequent events within a subject will be summarized descriptively in a separate display). Person-time at risk for each patient will be the length of the index exposure episode, defined as the number of days from the day after the index prescription start date to the last day of follow-up. For each outcome of interest, the crude incidence rate in each index exposure group is the number of incident events divided by the total number of person-years at risk and will be expressed per 100 person-years with 95% confidence intervals. The incidence rates for the SGLT-2i group and control group will then be compared using a hazard ratio and corresponding 95% confidence interval. This analysis will be performed using Cox proportional hazards regression or some other suitable method if the assumptions for the Cox model are not met.

An as-treated approach will be used for the primary analysis to account for additions or switches to the index assigned treatment. A grace period of the duration of last issued prescription will be applied. As a sensitivity analysis, an intent-to-treat approach will also be applied in which subjects will be analyzed according to the treatment they were originally assigned to, regardless of whether there were any subsequent treatment changes. Further details regarding both these approaches, including the censoring rules, potentially allowing for time varying factors and imputation of missing data, will be provided in the SAP.

Meta-analysis

A meta-analysis approach, based on the DerSimonian and Laird method [6], will be used where the hazard ratio point estimates for each country are pooled together to obtain an overall summary weighted point estimate. In this approach, random-effects models with inverse variance weighting for each country will be implemented. Up to a 1:3 treatment allocation ratio of SGLT-2i to control patients will be applied to ensure that there are enough SGLT-2i patients for analysis.

5.2 Bias

5.2.1 Methods to Minimize Bias

As this is an observational study, it is important to address and minimize potential sources of bias which may affect the interpretation of study results. One such bias that may occur is channeling bias which occurs when patients with certain baseline characteristics are more likely to be prescribed a certain treatment over another treatment. Hence, this may lead to differences in baseline characteristics between the treatment groups which may confound the relationship between the treatment group and the outcome, especially if the baseline characteristics are known to be correlated with the outcome. To address this potential source of bias, propensity scoring will be used to adjust for potential covariate differences between the treatment groups. Matching the patients in the SGLT-2i and comparator groups by the propensity score should minimize the potential confounding by these covariates.

5.2.2 Adjustment for Multiple Comparisons

Not applicable.

5.2.3 Strengths and Limitations

- This study will include data from multiple countries in order to increase the power of the analyses
- Because of the real world observational data, the population of this study will be more diverse compared to a randomized controlled trial and the results of this study will be more generalizable to a broader diabetes population.
- This study will provide some insight on the potential cardiovascular benefits of SGLT-2i/dapagliflozin ahead of the DECLARE study results.
- The set of core outcomes and variables will be limited to ensure as large as possible population
- The data in selected (to be selected) databases reflects everyday health care and is collected for non-research purposes. Therefore, clinical values are captured as part of routine clinical practice and there is considerable variation in the timing and completeness of measurements
- Some databases reports issued prescriptions only. In these cases, no information may be available as to whether the patient collected the prescription and used the product. However, if a product is repeatedly issued this most likely indicates that the medication is used.
- The index prescription i.e. the first prescription of a SGLT-2i medicine may not be the first ever SGLT-2i prescription for the patient in GP based EMR databases. For example, the first prescription may have been initiated by a consultant but then the

general practitioner will usually continue the care which could be a scenario in databases like CPRD and THIN.
- Will not be possible to define the outcome exactly equivalent to EMPA-REG as the databases will most likely not have all the required tests recorded
- Comparators will likely have earlier index dates to larger extent than SGLT-2i users and thus may have longer follow up
- Combination use of several of the classes of interest or a history of use of several of the classes of interest will occur and a classification of this will be assessed
- Patients may have limited persistence with their SGLT-2i treatment
- Cannot interpret statistical analyses from this study in the same way as could be done with a randomized clinical trial because this is an observational study
- The 1:3 treatment allocation ratio of SGLT-2i:other GLD patients may reduce the representativeness of the SGLT-2i patients selected for this study compared to the overall SGLT-2i patient population

5.3 Sample Size and Power Calculations

Power calculations

The primary endpoint will be hospitalization for heart failure. A risk reduction in this endpoint of 20% for the SGLT-2i group compared to the control group will be considered clinically meaningful. For 85% power to detect a risk reduction of 20% with a two-sided alpha level of 0.05, and up to 1:3 treatment allocation of SGLT-2i to the comparator arm, a total of 970 events will be needed across both treatment groups and all databases after the matched SGLT-2i and control groups have been created (Table 1). This calculation assumes the background rate of hospitalization for heart failure in the standard of care group is 0.625 events per 100 person-years and assuming a 20% reduction a rate of 0.5 events per 100 person years in the SGLT-2i group. For 1:3 treatment allocation, approximately 40,842 person-years will be needed in the SGLT-2i group and 122,526 person-years will be needed in the control group. However, the key driver for the power and the analysis is the number of events. The sample size is merely an approximation of how many person-years might produce the required number of events based on the assumed event rates. Also, the ratio of SGLT-2i: control matching may vary across the databases but as long as a total of 970 events are achieved, the analysis will be sufficiently powered.

The background rate of 0.625 events per 100 person-years is relevant for US, UK and Germany based on literature and empirical rates from the databases included in the study. Based on Swedish data, a substantially higher rate of 1.58 events per 100 person years has been observed. This difference in rates could be due to the age distribution and other factors including case ascertainment and baseline cardiovascular risk.

As there may not be enough statistical power for a standalone analysis in any of the individual country databases, a meta-analysis approach will be used to conduct the treatment comparison by pooling the hazard ratio estimates from all of the databases assuming that a total of 970 events have been observed. The higher rate of 1.58 events per 100 person years may apply in Sweden and the other Nordic countries. This higher event rate allows for the possibility of a sufficiently powered analysis in the Nordics alone. If 970 events have been observed in the Nordics, then a separate analysis will be submitted

for the Nordics database. Assuming 1:3 matching, approximately 16,019 person-years will be needed in the SGLT-2i group and 48,054 person-years will be needed in the control group to obtain the target of 970 events.

Table 1 displays the target number of events and total exposure time (in person-years) needed for the SGLT-2i and control groups under different estimates for risk reduction, power, and SGLT-2i: control treatment allocation ratios: :

Table 1. Exposure time needed for hospitalization for heart failure (person-years) if SGLT-2 rate is 0.5 events/100 patient-years.

Number of controls per SGLT-2i patient	Number of events			Total exposure time (SGLT-2i + control)			SGLT-2i exposure time		
30% reduction	**80**	**85**	**90**	**80**	**85**	**90**	**80**	**85**	**90**
1	255	290	340	42000	47765	56000	21000	23882	28000
3	340	380	460	51459	57514	69622	12865	14378	17405
5	470	545	610	69263	80316	89895	11544	13386	14982
25% reduction	**80**	**85**	**90**	**80**	**85**	**90**	**80**	**85**	**90**
1	385	440	515	66000	75429	88286	33000	37714	44143
3	520	600	700	83200	96000	112000	20800	24000	28000
5	710	790	940	111130	123652	147130	18522	20609	24522
20% reduction	**80**	**85**	**90**	**80**	**85**	**90**	**80**	**85**	**90**
1	635	730	850	112889	129778	151111	56444	64889	75556
3	850	970	1160	143158	163368	195368	35789	40842	48842
5	1160	1350	1520	192000	223448	251586	32000	37241	41931
15% reduction	**80**	**85**	**90**	**80**	**85**	**90**	**80**	**85**	**90**
1	1195	1370	1600	219622	251784	294054	109811	125892	147027
3	1620	1870	2120	286130	330286	374442	71532	82571	93610
5	2220	2500	2900	387077	435897	505641	64513	72650	84274

6. STUDY CONDUCT AND REGULATORY DETAILS

6.1 Data Management

6.1.1 Study Flow Chart and Plan

This study will be carried out internally to the largest extent possible. We will utilize the internal AZ access to Humedica. Combining THIN and CPRD data requires the analysis to be conducted by a contractor (CEIFE). The MarketScan data are analyzed by the Truven Health analytics.

The Swedish and Danish data (DAISY and DAFFODIL) will be updated with data on hospitalization diagnoses for 2015 which will be available in Q4 2016. Norwegian data (DAPHNE) is currently waiting to be delivered, estimated to November 2016. The Nordic/Baltic MC has access to all these databases and will conduct the analyses.
The German data (DPV) will be updated quarterly and the Q2 2016 data will be available September 2016.

The Canadian data will be received from The Manitoba Centre for Health Policy (MCHP), in Q4 2016 for part 1 and Q2 2017 for part 2. These data will be analyzed by researchers at the University of Manitoba and Seven Oaks Hospital, and not internally at AZ Canada.

6.1.2 Quality Control

All analyses will be conducted with the Statistical software SAS version 9.3 or higher, Stata and R. Quality control of coding and programming will be done according to the procedures applied for each database.

6.2 Protection of Human Subjects

Governance
Respective databases may have governance requirements in place to be allowed to use their data and publish the study results. This may require approval of the study protocol by external scientific bodies. For example the CPRD database studies will require Independent Scientific Advisory Committee (ISAC) approval and THIN database studies will require Scientific Committee Review (SCR) approval. The protocol will undergo internal scientific review by the MARC committee and require sign off by the GCL.

The final protocol of the Non-Interventional Study, including the final version of the Subject Informed Consent Form, must be approved or given a favorable opinion in writing by the Ethics Committee/Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

The Ethics Committee/IRB/IEC must also approve any amendment to the protocol and all advertising used to recruit subjects for the study, according to local regulations.

6.2.1 Subject Informed Consent

Not applicable since this is a secondary data study.

6.2.2 Confidentiality of Study/Subject Data

NIS data will be stored in a computer database, maintaining confidentiality in accordance with the local law for Data Protection.

6.3 Communication Plan

A Publications Steering Committee has been formed for the project consisting of leading researchers in the field of diabetes, public health and epidemiology from the US, UK and Sweden.

6.3.1 Publication Plan

A Non-Interventional Study Report will be prepared within 12 months after completion of the final analytic dataset as described in the Milestones section. If step 2 is conducted the Non-Interventional Study Report will incorporate both steps.

Results for Step 1 will be presented at relevant scientific conferences and full manuscripts will be developed for publication in biomedical journals. Step 2 results will also be presented at relevant scientific conferences and published as full manuscripts

All publications will adhere to the guidelines on publications in biomedical journals established by the International Committee of Medical Journal Editors (ICMJE) and published in its Uniform Requirements of Manuscripts Submitted to Biomedical Journals. Authorship and development of publications arising from this non interventional study will also adhere to AstraZeneca's Global Publications Policy and Standard.

6.3.2 Compliance with Study Registration and Results Posting Requirements

The study will be registered on clincialtrials.gov in accordance with AZ International Procedure 8-P43-cv-X, Disclosure of Trial Information on Public Websites.

The study is not a PASS-study (neither step1 or step 2) since the step 2 analysis will only be on class level for SGLT-2 inhibitors and not able to distinguish between different NYHA categories of heart failure. Step 2 will be registered on clinicaltrials.gov.

6.3.3 Compliance with Financial Disclosure Requirements

The AZ Standard Operating Procedures will be adhered to when engaging healthcare professionals or institutions in the project.

7. LIST OF REFERENCES

1. Zinman B et al. Empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes. NEJM 2015 sept 17 e pub ahead of print DOI: 10.1056/NEJMoa1504720
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5. Seong J-M et al. Differential cardiovascular outcomes after dipeptidyl peptidase-4 inhibitor, sulfonylurea, and pioglitazone therapy, all in combination with metformin, for type 2 diabetes: a population-based cohort study. PLOS one 201510(5):e0124287
6. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986; 7: 177-188.
7. Stuart E. Matching methods for causal inference: A review and a look forward. Stat Sci. 2010; 25: 1–21.
8. Fu A et al. Association between Hospitalization for Heart Failure and Dipeptidyl Peptidase 4 Inhibitors in Patients With Type 2 Diabetes: An Observational Study. Diabetes Care. 2016:39:726-34.

9. SIGNATURES

ASTRAZENECA SIGNATURE(S)

This protocol amendment concerns Step 2 of this study which will analyze the risk of cardiovascular (CV) outcomes and all-cause mortality in patients with type 2 diabetes mellitus (T2DM) who initiate use or treatment with sodium-glucose co-transporter-2 (SGLT-2) inhibitors compared to patients initiating other diabetes medications (other standard of care treatments). The study will use observational data from databases in US (Humedica, MarketScan), UK (CPRD, THIN), the Nordic countries (Sweden, Denmark and Norway), Germany and Canada.

I agree to the terms of this Non-Interventional Study protocol amendment.

AstraZeneca representative

Peter Fenici, Medical Affairs Lead *Medical Evidence Director/ Delegate/ Medical Director/Delegate/ NIS Study Leader* *peter.fenici@astrazeneca.com, +44 7818 524220*	Date (Day Month Year)

ASTRAZENECA SIGNATURE(S)

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I agree to the terms of this Non-Interventional Study protocol amendment.

AstraZeneca representative

Anna Maria Langkilde, *Global Clinical Lead dapagliflozin* *annamaria.langkilde@astrazeneca.com,* *+46 708 467699*	Date (Day Month Year)

ASTRAZENECA SIGNATURE(S)

This protocol amendment concerns Step 2 of this study which will analyze the risk of cardiovascular (CV) outcomes and all-cause mortality in patients with type 2 diabetes mellitus (T2DM) who initiate use or treatment with sodium-glucose co-transporter-2 (SGLT-2) inhibitors compared to patients initiating other diabetes medications (other standard of care treatments). The study will use observational data from databases in US (Humedica, MarketScan), UK (CPRD, THIN), the Nordic countries (Sweden, Denmark and Norway), Germany and Canada.

I agree to the terms of this Non-Interventional Study protocol amendment.

AstraZeneca representative

Niklas Hammar, *Senior Director Epidemiology CVMD*	Date (Day Month Year)

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Appendix 1. Power calculations for the secondary outcome all-cause mortality

The power calculations for the secondary outcome, all-cause mortality, are included in the table below based on a statistical power of 85% and for three scenarios with 15%, 20% and 25% risk reduction respectively. These calculations are based on a rate of all-cause mortality estimate of 0.84/100 person-years in the SGLT2 group based on CPRD data. Table 2 displays the number of person-years required in each treatment arm given either one or three controls per SGLT-2i user.

Table 2. Exposure time needed for all-cause mortality (person-years) if SGLT-2i rate is 0.84 events/100 patient-years.

Number of controls per SGLT-2i patient	Control exposure time	SGLT-2i exposure time
15% risk reduction	**85**	**85**
1	70135	70135
3	138775	46258
20% risk reduction	**85**	**85**
1	38858	38858
3	72933	24310
25% risk reduction	**85**	**85**
1	24002	24002
3	16784	5594