[redacted]

Statistical and Epidemiological Analysis Plan

BI Trial No.:	1245.195
Title:	**Multi-country non-interventional study on the effectiveness of Empagliflozin in adult patients with type 2 diabetes in Europe and Asia.**
Responsible trial statisticians:	[redacted]
Responsible project epidemiologists:	[redacted]
Date of statistical and epidemiological analysis plan:	22 November 2019
Version:	2.0

1 TABLE OF CONTENTS

2 LIST OF TABLES

3 LIST OF ABBREVIATIONS

Term	Definition/description
ACE	Angiotensin-converting-enzyme
ACM	All-cause mortality
ARB	Angiotensin II receptor blocker
AT	As-treated
BI	Boehringer Ingelheim International GmbH
BNP	B-type natriuretic peptide
BUN	Blood urea nitrogen
CABG	Coronary artery bypass grafting
CHF	Congestive heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CV	Cardiovascular
CVM	Cardiovascular mortality
DPP-4	Dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate
ESRD	End-stage renal disease
GLP-1	Glucagon-like peptide-1
GP	Grace period
HbA1c	Glycated hemoglobin
HCRU	Healthcare resource utilization
HDL	High-density lipoprotein
HHF	Hospitalization for heart failure
HONK	Hyperosmolar hyperglycemic nonketotic syndrome
ICD-10	International Classification of Diseases, 10^{th} version
ITT	Intention to treat
LDL	Low-density lipoprotein
MA	Marketing authorization
MACE	Major adverse cardiovascular event
MI	Myocardial infarction

NSAID	Nonsteroidal anti-inflammatory drug
NT	N-terminal
PCSK-9	Proprotein convertase subtilisin/kexin type 9
PS	Propensity score
PTCA	Percutaneous transluminal coronary angioplasty
SAP	Statistical analysis plan
SD	Standard deviation
SE	standard error
SGLT-2	Sodium-glucose cotransporter-2
Std	Standardized difference
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TIA	Transient ischemic attack

4 INTRODUCTION

This statistical analysis plan (SAP) describes the planned meta-analysis and refers to the final version of the master protocol of the study entitled "Multi-country non-interventional study on the effectiveness of empagliflozin in adult patients with type 2 diabetes in Europe and Asia", version *1.1* dated *13 SEP 2019* unless otherwise stated. According to the master protocol, non-interventional, cohort study using existing data will be carried out in eleven countries.

The overall objective of this study is to examine effectiveness, safety, health care resource utilization (HCRU), and cost of care outcomes associated with the use of empagliflozin or any sodium-glycose cotransporter-2 (SGLT-2) inhibitors, compared with the use of dipeptidyl peptidase-4 (DPP-4) inhibitors, among adults with type 2 diabetes mellitus (T2DM).

The eleven country-specific results of effectiveness and safety outcomes will be pooled together via meta-analysis methods. In addition, the results regarding HCRU and cost outcomes will be collected together and presented side-by-side from each country. Results of HCRU outcomes will also be pooled via meta-analysis methods for countries where healthcare systems are comparable. Results of cost outcomes will not be pooled using meta-analysis methods as healthcare cost levels vary in wide ranges among countries. This SAP describes detailed statistical methodology used in the meta-analyses.

5 CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Amendment number	Date	Sections of the SAP	Amendment or update	Reason
1	22 NOV 2019	Multiple	New renal and safety outcomes included.	To demonstrate an association of the study drug and the relevant safety outcomes.
		6.1, 10.2, 10.3	Emergency room visits will be analyzed as a separate outcome from outpatient visits in HCRU analyses and in cost analyses	To be consistent with protocol amendment
		7.1	Exposure section clarified.	To improve on clarity after addition of renal and safety outcomes.
		7.3, 7.4	Update of the inclusion/exclusion criteria.	To be consistent with the protocol amendment.
		7.3, 8.7, 10.3	Safety outcomes, HCRU and cost of care outcomes will be analyzed exclusively for empagliflozin as the exposure group and DPP-4 inhibitors as the comparison group.	To have drug-specific safety outcomes and healthcare utilization and costs .
		[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	
		7.6	Study time-windows clarified.	To improve on clarity
		[redacted]	[redacted]	
		8.5.2, 10.3	Added meta-analysis for HCRU in countries with comparable healthcare systems	To enable general results of HCRU outcomes
		10.2, 10.3	Added average length of stay as HCRU outcome	To estimate the association of the length of hospitalization and the use of glucose lowering drugs
		10.2	HCRU outcomes will be presented per member per year instead of month	To be consistent with regional standards
		Multiple	Description of possible data of drug usage made more general.	To improve on clarity
		Multiple	Minor changes.	To make SAP consistent with the protocol updates.

6 OUTCOMES

6.1 MAIN OUTCOMES

The primary effectiveness outcomes are:

1. Hospitalization for heart failure,
2. All-cause mortality,
3. Composite outcome including
    - Hospitalization for heart failure,
    - All-cause mortality,
4. Myocardial infarction (MI),
5. Stroke,
6. Composite outcome including
    - MI,
    - Stroke,
    - All-cause mortality.

The secondary cardiovascular effectiveness outcomes are:

1. Cardiovascular (CV) mortality,
2. Composite outcome including,
    - Hospitalization for heart failure,
    - CV mortality,
3. 3-point major cardiovascular event (MACE), a composite outcome including
    - MI,
    - Stroke,
    - CV mortality,
4. Coronary revascularization procedure.

The secondary renal effectiveness outcomes are:

1. End-stage renal disease (ESRD),
2. Estimated glomerular filtration rate (eGFR) decline,
    (a) Decline from normal kidney function (≥60ml/min/1,73m^2) to abnormal kidney function (<60ml/min1,73m^2).
    (b) Change in eGFR over time.
3. Progression from normoalbuminuria to micro- or macroalbuminuria,
4. Composite outcome of abnormal renal function including,
    - eGFR decline
    - progression from normoalbuminuria to micro- or macroalbuminuria.

The secondary safety outcomes are:

1. Bone fracture,
2. Diabetic ketoacidosis,
3. Severe hypoglycemia,

4. Lower-limb amputation,
5. Acute kidney injury requiring dialysis.

The secondary HCRU outcomes are:

1. Number of all-caused inpatient healthcare visits (hospital admissions) during the follow-up,
2. Number of all-caused outpatient healthcare visits during the follow-up excluding emergency room visits,
3. Number of all-caused emergency room visits,
4. First inpatient stay (as time to event outcome),
5. Number of Inpatient days during the follow-up,
6. Average length of stay of hospital admission.
7. Number of dispensations/other records of the drug use during the follow-up.

The secondary healthcare cost outcomes are:

1. Total healthcare costs during the follow up,
2. Inpatient healthcare costs during the follow up,
3. Outpatient healthcare costs during the follow up, excluding costs related to emergency room visits,
4. Costs of emergency room visits.
5. Pharmacy costs during the follow up.

Master definitions of all the outcomes are provided in the master protocol. Detailed definitions of these outcomes will be described in the localized protocols and will be collected using appendix 2.

[redacted]

6.3 OTHER VARIABLES

Data from each country-specific study will be collected at baseline as specified in Tables 3 and 4 of Appendix 1. Types of these baseline covariates are briefly summarized in Table 1. General definitions of these variables are listed in Annex 7 of the master protocol. Detailed definitions of these variables may vary by country and will be collected using respective template (Appendix 2).

Table 1. Types of covariates at baseline.

Covariate type	**Measurement period**
Sociodemographic characteristics	Index date (closest to)
Covariates related to lifestyle	Index date (closest to)
Diabetes complications	12 months preceding index date (inclusive)
Other comorbidities	12 months preceding index date (inclusive)
Laboratory values	12 months preceding index date (inclusive)
Prior/concomitant use of other antidiabetic drugs	12 months preceding index date and at index date
Prior use of other drugs	12 months preceding index date (inclusive)
HCRU covariates	12 months preceding index date (inclusive)
Cost covariates	12 months preceding index date (inclusive)

7 GENERAL ANALYSIS DEFINITIONS

7.1 EXPOSURE

The main exposures in this study are incident use of empagliflozin and incident use of any SGLT-2 inhibitor. The main comparator is incident use of any DPP-4 inhibitor during the study period. [redacted]

Drug use will be assumed to begin on the date of a dispensation or the date of any other record of the drug use. A supply will indicate the duration of exposure after a dispensation or any other record of the drug use. If a subsequent supply occurs before the previous supply has finished, the start of the subsequent supply will be shifted. To avoid artificially long exposure periods, however, a subsequent supply can be shifted with a maximum of 14 days, which is considered a reasonable time for patients to refill prior to the end of their ongoing supply. A grace period (GP) for 100% of the duration of the most recent supply will be included in the exposure period to account for uncertainty related to actual drug use patterns. Overlapping supplies and grace periods will be combined as exposure periods. The grace period will be defined from the most recent supply. If the grace period reaches the next supply, the exposure continues.

In the main analyses an 'as-treated' (AT) approach will be utilized. In the AT approach the follow-up is censored at discontinuation of continuous exposure, switch to another study drug or at start of a concomitant use with another study drug (any SGLT-2 inhibitor or any DPP-4 inhibitor). The outcomes related to effectiveness, safety, HCRU, and the cost of care will be observed until the end of the first continuous exposure to a study drug, death, end of data availability or end of the study period. If patient's usage of the study drug ends (grace period taken into consideration) and starts again later, the later usage is not taken into account in the analyses. The grace period will only be applied if the subsequent drug is not one of the study drugs (any SGLT-2 inhibitor or any DPP-4 inhibitor). Otherwise we define the event as a switch or start of the concomitant treatment and the exposure is censored immediately at the date of first dispensation or other record of initiating another study drug or a concomitant use (see Figure 1 for details).


[redacted]

Depending on the data source, the end of data availability could result from, for example moving to another region or admission to institutional care. The end of data availability is a patient level reason for censoring the exposure while the end of stuy period depends on the general data availability in each country (not later than December 2018).

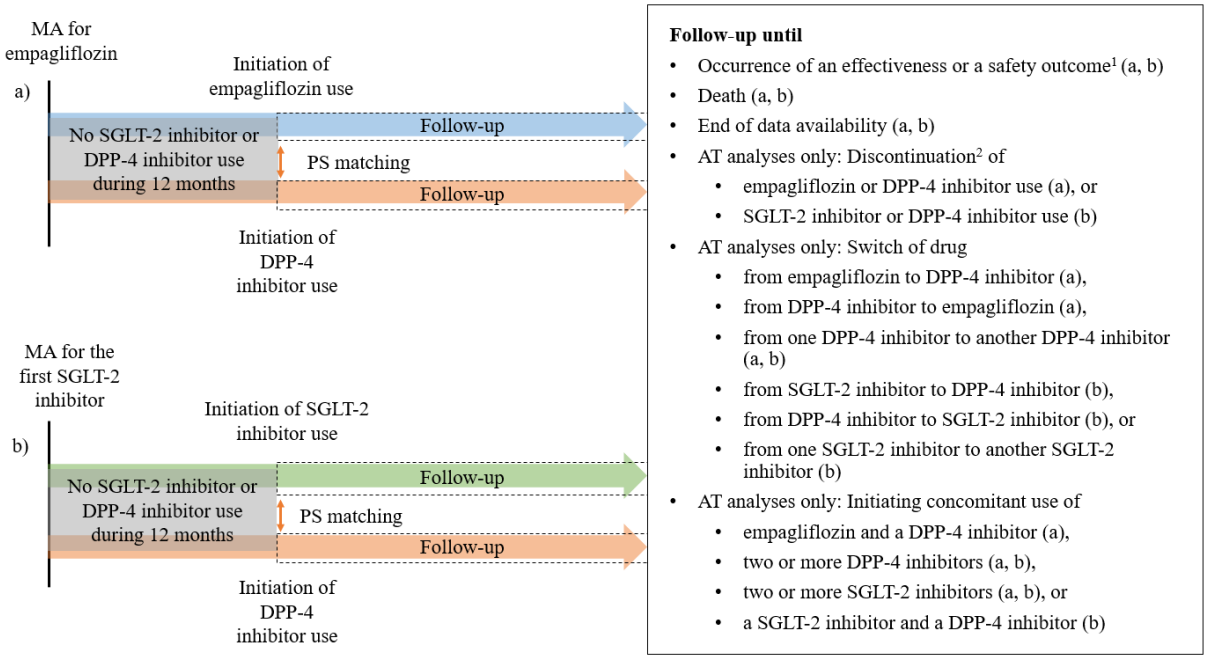
When investigating the safety outcomes, a modified AT approach will be utilized in the main analyses with an additional exposure risk window of 30 days after discontinuation of drug use, to consider potential lag in the occurrence of safety outcomes. Consequently the risk period in these analyses will consist of the supply, grace period and exposure risk window. The exposure risk window will be accounted for only if the follow-up ends at discontinuation of drug use but

not at discontinuation for any other reason (including switch to another study drug or starting concomitant use with another study drug).

Figure 1. Overview of the study periods and comparison pairs in the analyses:

a) Analyses comparing empagliflozin use with DPP-4 inhibitor use;

b) Analyses comparing SGLT-2 inhibitor use with DPP-4 inhibitor use.



AT= as treated; DPP-4= dipeptidyl peptidase-4; MA= marketing authorization; PS= propensity score; SGLT-2= sodium-glucose cotransporter-2.

[1] In analyses investigating effectiveness or safety outcomes, the occurrence of the outcome in question will be observed until the end of the follow-up (e.g. while investigating hospitalization for heart failure, the follow-up will not end at the occurrence of a stroke).

[2] In analyses investigating safety outcomes, an exposure risk window will be accounted for after discontinuation.

7.2 DEVIATIONS FROM THE PROTOCOL

1. Meta-analysis for HCRU outcomes in countries with comparable healthcare systems was decided to be added in the SAP
2. HCRU outcomes will be presented per member per year instead of per member per month
3. Conditional re-matching for renal outcome analysis will be performed based on data.

7.3 PATIENT SETS ANALYZED

Separate studies following the master protocol will be carried out in the following eleven countries: Denmark, Finland, Germany, Israel, Japan, Norway, South Korea, Spain, Sweden, Taiwan and the United Kingdom. All the studies in different countries will use three main sub-cohorts: i) Patients with diagnosed T2DM who initiated the use of empagliflozin, ii) patients with diagnosed T2DM who initiated the use of any SGLT-2 inhibitor, and iii) patients with diagnosed T2DM initiating the use of any DPP-4 inhibitor. When investigating effectiveness outcomes (primary and secondary), both exposed sub-cohorts, empagliflozin and any SGLT-2 inhibitor users will be compared with the comparator sub-cohort (any DPP-4 inhibitor users). For safety, HCRU and costs of care outcomes, the main exposure of interest is exclusively empagliflozin, and thus SGLT-2 inhibitor users will not be analyzed.

For meta-analyses, it is preferable that the country-specific analyses sets are as similar as possible according to inclusion/exclusion criteria. The master protocol states the following criteria:

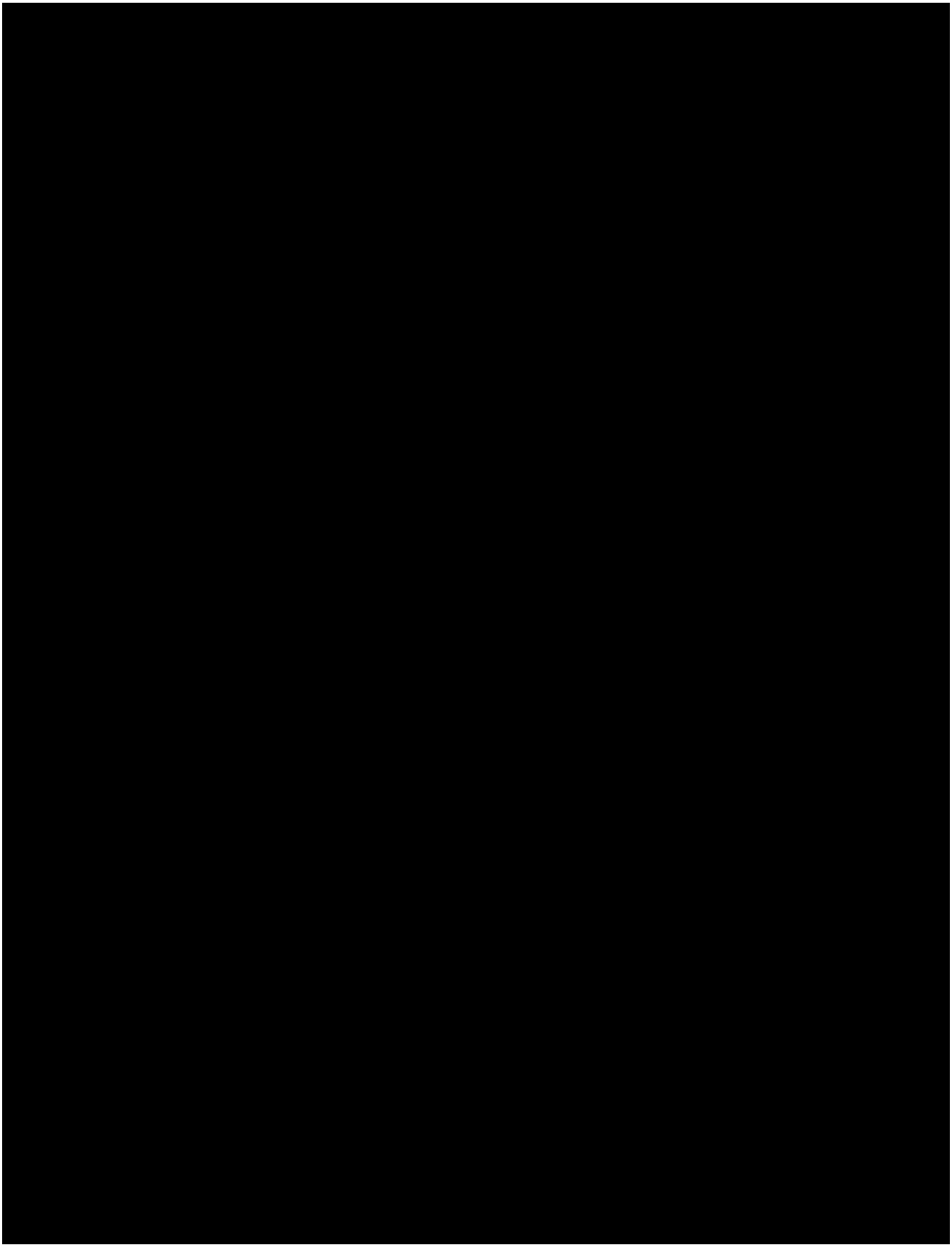
Inclusion criteria:

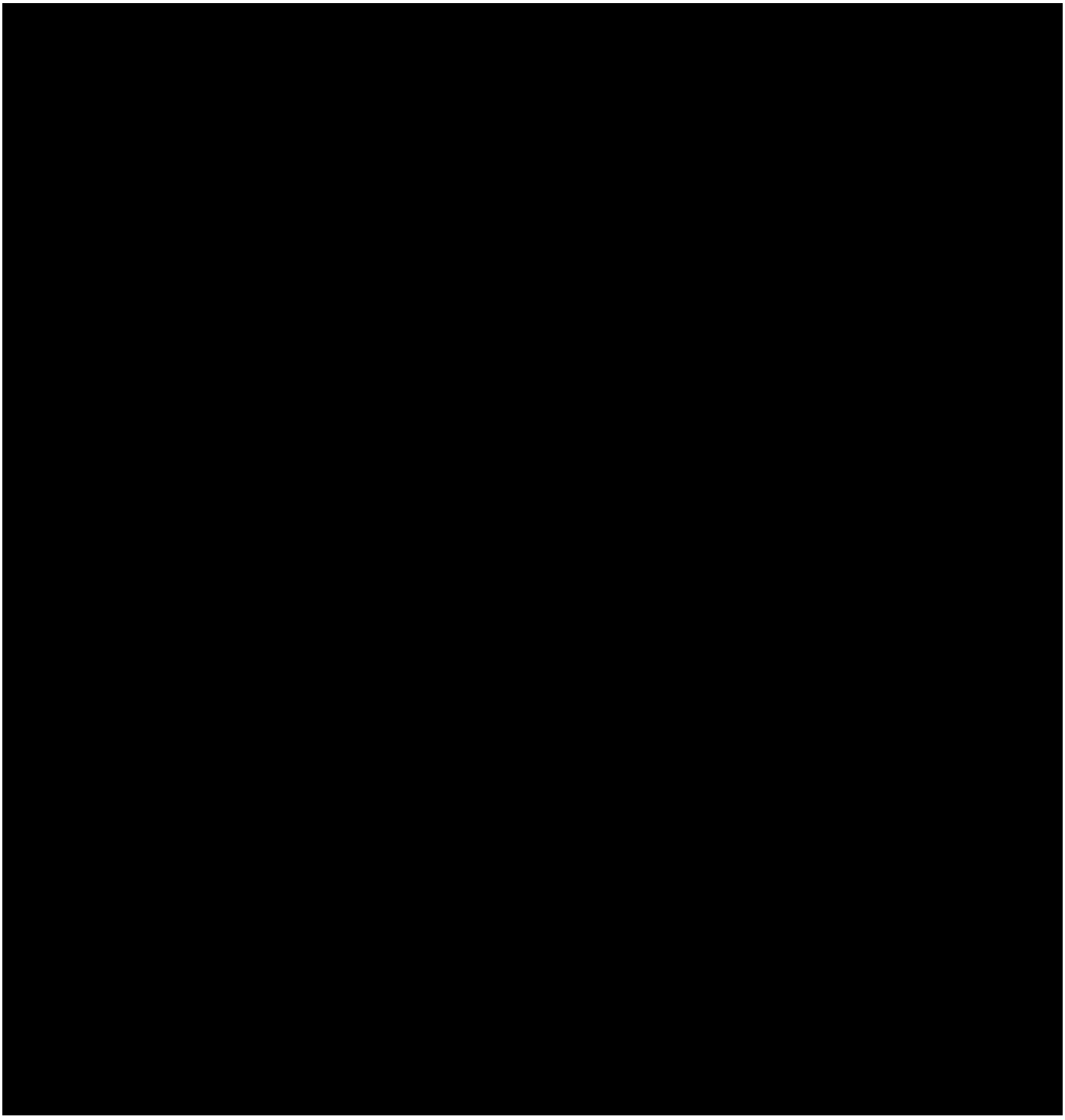
1. Dispensation or any other record of empagliflozin, any SGLT-2 inhibitor or any DPP-4 inhibitor use during the study period,
2. No dispensation or any other record of any other SGLT-2 inhibitor or DPP-4 inhibitor use (including possible SGLT-2 inhibitors or DPP-4 inhibitors that are marketed locally and are not study drugs of this multi-country study) during the 12 months preceding the index date (patients are also excluded if they are at the index date dispensed both a SGLT-2 inhibitor and a DPP-4 inhibitor, or if records of use are available for both, in free or fixed-dose combination),
3. Having a diagnosis of T2DM before the index date based on International Classification of Diseases, 10th version (ICD-10) codes or other available data.

Exclusion criteria

1. Aged <18 years on the first dispensation date or date of the first record of empagliflozin, any SGLT-2 inhibitor or any DPP-4 inhibitor use,
2. Pre-existing diagnosis of type 1 diabetes mellitus (T1DM) during the 12 months before the index date,
3. Pre-existing diagnosis of secondary diabetes or gestational diabetes in the 12 months prior to the index date,
4. Having a diagnosis of ESRD during the 12 months before the index date,
5. <12 months of available data before the index date, and/or no complete history of drug dispensation/other records of drug use during this period, and
6. Missing or ambiguous data on age or sex.

The country-level data on the included patients in all analyses will be collected using respective templates (see Appendix 1).





7.5 HANDLING OF MISSING DATA AND OUTLIERS

If a country is not able to provide specific pre-defined results needed in a particular meta-analysis, it will be excluded from that analysis.

Available covariate data for model adjustments in the country-specific analyses will be collected from each country (Appendix 1, table 5). Planned covariates that are missing from the analyses will be reported.

7.6 BASELINE, TIME WINDOWS AND CALCULATED VISITS

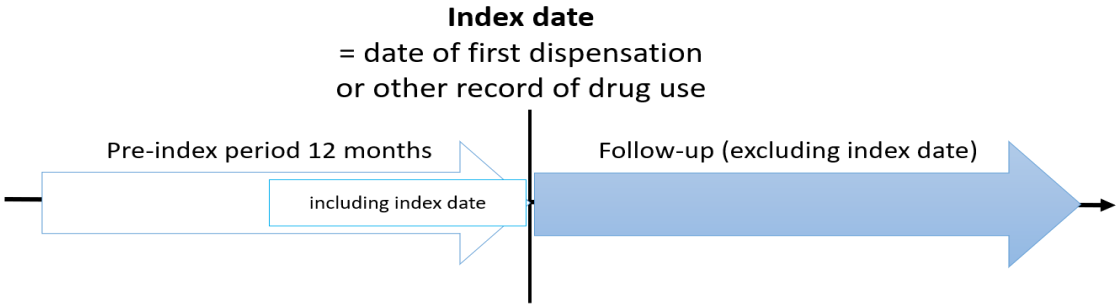
The study period in each country starts from the marketing authorization (MA) date of the exposure drug (empagliflozin or any SGLT-2 inhibitor). For all PS-matched patients the follow-up period starts on the index date. The index date for exposed patients (initiating empagliflozin or any SGLT-2 inhibitor) is defined as the date of the first dispensation or any other record of use of the sub-cohort-defining drug after marketing authorization date. For the comparison sub-cohort, the index date is defined as the date of the first dispensation or any other record of the DPP-4 inhibitor use during the study period. The follow up-time ends with the first occurrence of any of the following events: occurrence of a respective effectiveness or safety outcome (when studying outcomes related to effectiveness or safety), death, discontinuation of the initial drug use, switch to any other study drug (empagliflozin, any SGLT-2 inhibitor, any DPP-4 inhibitor (including drugs that are marketed locally and are not study drugs in this multy-country studies)), initiation of concomitant use of empagliflozin/SGLT-2 inhibitor and a DPP-4 inhibitor use (including drugs that are marketed locally and are not study drugs in this multy-country study) or drugs within the same class (i.e. two SGLT-2 inhibitors or two DPP-4 inhibitors) either as free or fixed dose combination, end of availability of data or end of the study period. Depending on the data source, the end of data availability could result from, for example, moving to another region or admission to institutional care. When studying the HCRU and cost of care outcomes, the follow-up is not censored at the occurrence of an effectiveness or a safety outcome.

If the follow-up ends at the index date, the patient will not contribute to the outcome analyses, i.e., that patient will account for 0 person-years and 0 events, even if follow-up ended due to an outcome happening at the index date (e.g. death). The minimum follow-up time will be 1 day for each patient who contributes to the outcome analyses, and the follow-up time contributing to the analyses starts one day after the index date. Specifically, follow-up time will be 1 day for any patient whose follow-up ends at the day following the index date i.e., the formula for computing the duration of follow-up is as follows: date of the end of the follow-up – the index date (Figure 2).

Each person will be included only once in each sub-cohort.

Baseline period for collecting covariate data prior to index date is at minimum 12 months, i.e., data must be available at minimum of 12 months for all patients. For comorbidities, data from further history may be used, depending on the country. To determine prior, concomitant or current use of other antidiabetic drugs, exactly 12 months prior to index date including the index date will be used. In the current use definition of other drugs, the supply must overlap with the index date. Baseline period for collecting prior use of other drugs is also exactly 12 months.

Figure 2. Definitions of pre-index and follow-up period for all who contribute to the outcome analyses.



8 PLANNED ANALYSIS

8.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The sociodemographic, lifestyle and laboratory characteristics of study sub-cohorts after propensity score (PS)-matching will be collected at baseline, separately from each country, using tables 3 and 4 in Appendix 1. If a laboratory variable has been measured multiple times during 12 months prior to the index date, the most recent value will be used. The output will be presented in a descriptive table outlined in Table 2 of section 10.2, presenting different countries side by side. Separate output table for each exposure drug (empagliflozin or any SGLT-2 inhibitors) and for each possibly different matched cohort will be presented. Separate tables for renal outcomes 2-4 will be presented based on the analysis-ready cohort.

Baseline HCRU and healthcare cost variables will be collected using tables 3 and 4 in Appendix 1. The output will be presented in a descriptive table outlined in Table 3 of section 10.2, presenting countries side by side. Separate output table for each exposure drug (empagliflozin or SGLT-2 inhibitors) and for each possibly different matched cohort will be presented. Separate tables for renal outcomes 2-4 will be presented after additional exclusion of patients.

For the purpose of examining the balance of the covariates between the two compared sub-cohorts after the PS-matching, the standardized differences (Std) for all the baseline variables will be also given in the descriptive tables. The formula for standardized difference for a dichotomous covariate is

$$d = \frac{|p_1 - p_2|}{\sqrt{\frac{p_1(1-p_1) + p_2(1-p_2)}{2}}},$$

where p_1 and p_2 denote the prevalence in exposed and unexposed patients, respectively. For a continuous variable, the formula is:

$$d = \frac{|\overline{x_1} - \overline{x_2}|}{\sqrt{\frac{s_1^2 + s_2^2}{2}}},$$

where $\overline{x_1}$ and $\overline{x_2}$ denote the sample means; s_1^2 and s_2^2 sample variances in exposed and unexposed patients respectively. For categorical variable with multiple levels, the method proposed by Dalton [1] will be used.

8.2 CONCOMITANT DISEASES AND MEDICATIONS

Baseline characteristics such as diabetes complications, comorbidities, use of non-diabetic drugs and prior/concomitant use of antidiabetic drugs during 12 months preceding index date and at index date will be collected (Appendix 1, tables 3 and 4). The output will be presented in a descriptive table outlined in Table 4 of section 10.2, presenting countries side by side. Separate output table for each exposure drug (empagliflozin or SGLT-2 inhibitors) and for each possibly different matched cohort will be presented. Separate tables for renal outcomes 2-4 will be presented based on the analysis-ready cohort.

Distribution of the index drug in each sub-cohort will be collected from each country using table 6 of Appendix 1, separately for each exposure sub-cohort (empagliflozin or any SGLT-2 inhibitor) and each possibly different matched cohort. The output will be presented in a descriptive table outlined in Table 5 of section 10.2, presenting countries side by side. A separate output table for each exposure drug (empagliflozin or any SGLT-2 inhibitor) and for each matched cohort will be presented. Separate tables for renal outcomes 2-4 will be presented based on the analysis-ready cohort.

8.3 METHODS ADDRESSING BIAS

The master protocol states PS-matching and covariate adjustment as methods to minimize bias within each study country. As part of the meta-analyses, the potential for residual confounding will be investigated, based on the results of the success of PS-matching and covariate adjustment. Subsequently, each country will be evaluated to be in either low, medium or high risk of bias. These evaluations will be based on the following considerations:

- Covariate availability (are all protocol-defined covariates available?),
- Covariate adjustment (have all covariates been used in the adjustments as described in the master protocol?),
- Success of matching by investigating the covariate balance after PS matching and PS distribution before and after matching,
- Other deviations from the master protocol, including exposure and outcome definitions in particular,
- Results of sensitivity analyses conducted (are results sensitive to changes applied in the sensitivity analyses, and why?),
- Data availability for sufficient follow-up time (does follow-up time differ across comparison groups and should censoring be regarded as informative?)
- Differences in index drug distribution (are there any differences in individual SGLT-2 or DPP-4 drug prescription patterns across countries?).

The results of these assessments will be presented in a table outlined in Table 7 of section 10.2.

[redacted].

8.4 METHODS ADDRESSING CONFOUNDING/EFFECT MEASURE MODIFICATION

As stated above, the master protocol states PS-matching and covariate adjustment as methods to control for confounding. In addition, the master protocol defines subgroup analyses as methods to control for effect modification. [redacted]

[redacted]

8.5 MAIN ANALYSES

8.5.1 Assessment of heterogeneity

Prior to conducting meta-analyses, heterogeneity across the countries in terms of study design and conduct will be assessed by considering deviations from the master protocol for each country. Specifically, the variability in participant factors (baseline characteristics, study drug exposures), use of covariates in PS and regression models will be investigated. Statistical heterogeneity will be subsequently assessed using:

- The estimated total heterogeneity.
- The Chi-squared test for heterogeneity (significance level: 0.1, null-hypothesis: no heterogeneity exists).
- I^2 statistic (0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity).

In process of assessment of the existence of the heterogeneity, I^2 and the p-value of the test of heterogeneity will be looked together and the following criteria will be used: I^2 values less than 50% indicates heterogeneity level of none to moderate and I^2 values 50% or greater indicate that heterogeneity level is moderate to considerable [2][3]. In case of $I^2 >= 50\%$ or $P<0.1$ (Chi-squared test), the study design and characteristics in the included sub-studies will be reviewed and the possible source of heterogeneity discussed, including but not limited to the following points:

- Covariate adjustment in models: Data about availability of covariates and usage in models will be collected (Appendix 1, table 5).
- Success of matching: Baseline after-matching characteristics will be collected together with standardized differences (Appendix 1 tables 3 and 4). In addition, figures that illustrate propensity score distribution among the main exposure sub-cohorts (empagliflozin/any SGLT-2 inhibitor) and among the comparator sub-cohort (any DPP-4 inhibitor) before and after each PS-matching will be collected (example in Figure 4 in section 10.1). [redacted]
- Data availability for sufficient follow-up time: Total follow-up times and number of patients in every sub-cohort will be collected (Appendix 1 table 7) and evaluated.
- Differences in index drug distribution: Drug distribution data will be collected for every different PS-matched cohort (Appendix 1 table 6). Differences in these distributions across countries can lead to heterogeneity.
- Other deviations from the protocol: Data flowchart in terms of numbers of patients will be collected for each country (Appendix 1 table 14) and presented

in comparative table outlined in Table 8 of section 10.2. Data describing the coding system used to define comorbidities, exposures and outcomes will be also collected (Appendix 2).

8.5.2 Meta-analyses

Separate analyses results for each main exposure sub-cohort (empagliflozin/any SGLT-2 inhibitor) and for each effectiveness and safety outcome will be collected from the countries using tables 1 and 2 in Appendix 1 and pooled together using random effects meta-analysis model. Results for HCRU outcomes will be collected using tables 8 and 11 in Appendix 1 and pooled together using random effects meta-analysis model for specific countries which have similar healthcare systems (European countries, Asian countries, Nordic countries). [redacted] The results will be presented in a forest plot including the following information:

- Study identifiers.
- Effect size and 95% CI for each study included in the analysis (on log scale).
- The weights allocated to each study.
- The combined estimated effect size with 95% CI (on log scale).
- The estimated effect size using fixed effect model.
- Estimated amount of heterogeneity (τ^2).
- Value of the Chi^2 test statistic, with number of degrees of freedom and p-value.
- The proportion of variability explained by heterogeneity (I^2).
- The value of the Z score for overall effect with p-value.

An example of the result output is given in Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.** of section 10.1.

[redacted]

[redacted]

8.8 QUALITY CONTROL

The meta-analysis will be conducted as described in study related documents (SAP and master protocol). The principal investigator, co-investigators and the Sponsors of the study must approve all revisions to the study documents. All changes to the study documents must be properly documented as protocol or SAP amendments.

A quality control will be performed on the aggregate data from each country. If data are missing or incorrect, the dataset is sent back to the local contact points for correction. Such quality control includes (but is not limited to):

- Comparing the exposure times between AT and ITT approach,
- Comparing the exposure times between different grace period (GP) values,
- Comparing the number of events between AT and ITT approach,
- Comparing the number of events between different GP values,
- Comparing the number of events between different exposure risk window values,
- Checking that sub-cohort sizes in different comparisons match,
- Checking that composite outcomes have more events than their individual components,

All programs for data management and data analyses will be written by study statistician(s). Quality control check of these programs will be carried out by a statistician other than the one who writes the programs. All processes from data management leading to dissemination of

study results will undergo quality control checks for programs, result tables and written text. A detailed audit trail of all documents (programs, result tables, reports) along with quality control processes will be maintained.

8.9 EXPOSURE TIME

The number of patients with events, the respective accumulated exposure times and the number of patients at risk will be collected from each country using table 7 of Appendix 1. The output will be presented in a descriptive table outlined in Table 6 of section 10.2, presenting countries side by side. Separate table will be presented for each effectiveness and safety outcome and comparison drug (empagliflozin or any SGLT-2 inhibitor), in all possibly different matched cohorts.

8.10 SAFETY ANALYSIS

Not applicable.

8.10.1 Adverse events

8.10.2 Laboratory data

8.10.3 Vital signs

8.10.4 ECG

8.10.5 Others

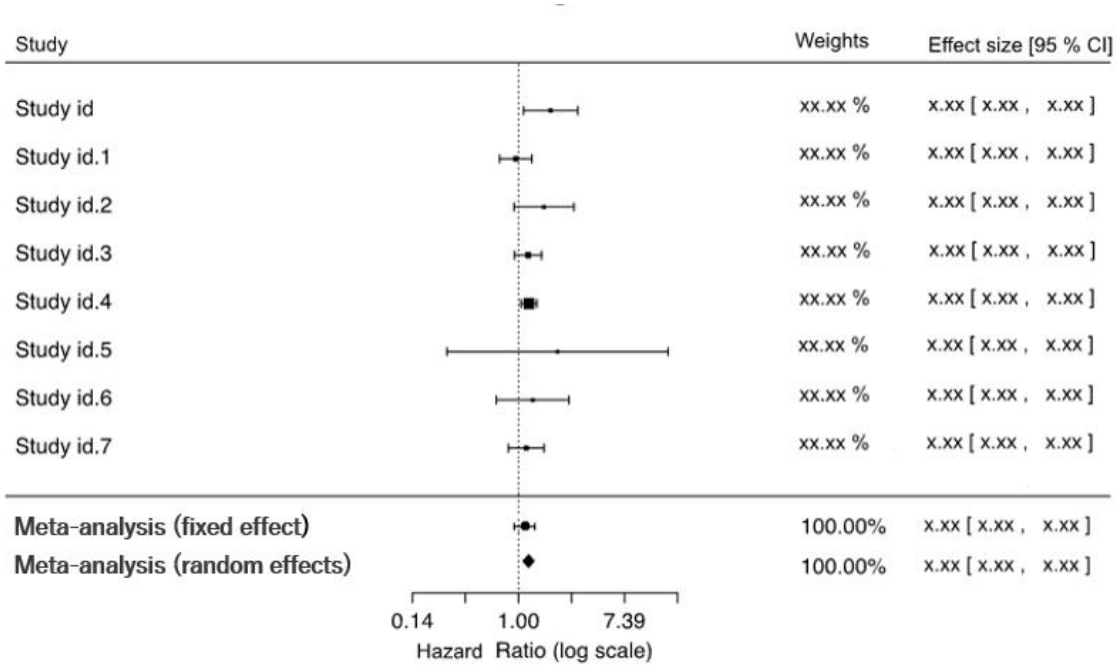
9 REFERENCES

1. Dongsheng Yang, Jarrod E. Dalton. A unified approach to measuring the effect size between two groups using SAS. http://support.sas.com/resources/papers/proceedings12/335-2012.pdf
2. Higgins JPT, Thompson SG, Deeks JJ, Altman DG, Measuring inconsistency in meta-analyses. *BMJ* 2003; 327; 557-560.
3. Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. URL http://www.handbook.cochrane.org.

10 ADDITIONAL SECTIONS

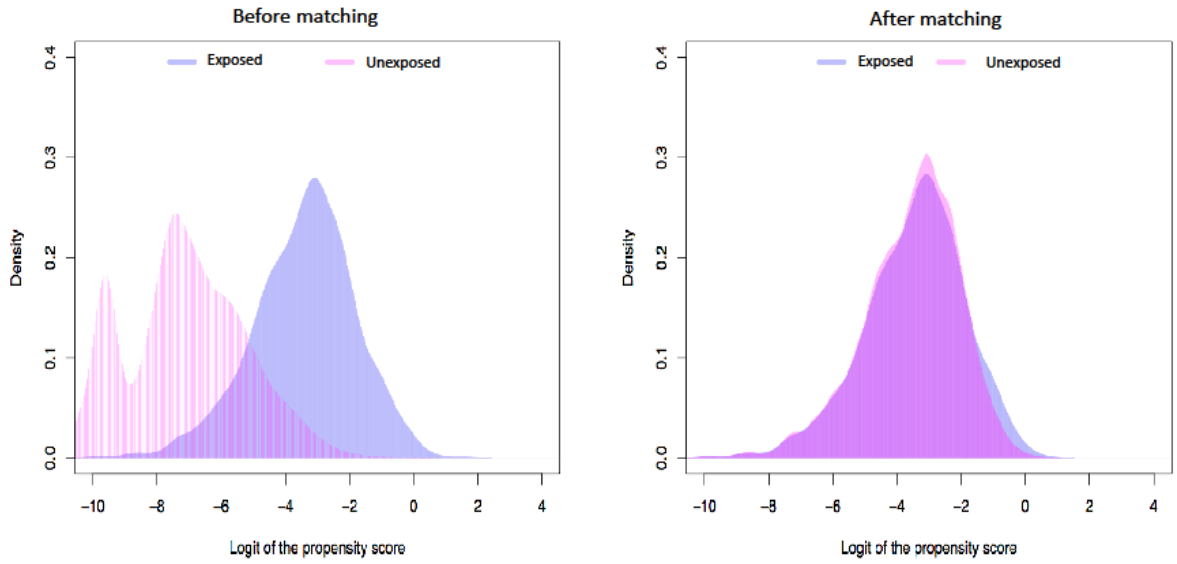
10.1 FIGURE SHELLS

Figure 3. Illustration of the main meta-analysis results.



Heterogeneity: Q (df=) = xxx.xx, p-value = x.xxx, I^2 = xx.xx %, τ^2= xx.xx.
Z=x.xxx , p-value = x.xxx .

Figure 4. Illustration of propensity score distribution among the main exposure sub-cohort ("exposed") and among the comparator sub-cohort ("unexposed") before and after the matching in [main/subgroup analyses].



10.2 TABLE TEMPLATES FOR RESULT OUTPUTS

Table 2. Baseline (closest to the index date) summaries for demographic variables, lifestyle variables and laboratory values in after-matching cohort in [main/subgroup analyses] comparing the main exposure sub-cohort (empagliflozin/any SGLT-2 inhibitor; separate table for each) and the comparator sub-cohort (any DPP-4 inhibitor).

Variable	Country 1			Country 2			Country 3		
	Main exposure sub-cohort	Comparator sub-cohort	Std	Main exposure sub-cohort	Comparator sub-cohort	Std	Main exposure sub-cohort	Comparator sub-cohort	Std
Number of patients	n	n		n	n		n	n	
Demographic variables									
Age at index									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	Xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
18-44	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
45-54	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
55-64	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
65-74	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
75+	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Sex									
Female	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Male	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-

Race									
Category 1	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Category 2	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Category 3	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Socioeconomic status									
Low	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
intermediate	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
high	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Calendar year of the index date									
2012	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
2013	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
2014	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
2015	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
2016	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
2017	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
2018	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Lifestyle variables									
Obesity									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-

Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Overweight									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Smoking									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Alcohol abuse or dependence									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Drug abuse or dependence									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Laboratory values									
HbA1c (%)									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	Xx	xx	-	xx	xx	-

Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
LDL level (mg/dl)									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	Xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
HDL level (mg/dl)									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	Xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Total cholesterol (mg/dl)									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	Xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-

Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Triglyceride level (mg/dl)									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	Xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Creatinine (mg/dl)									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	Xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Glomerular Filtration Rate (mL/min/1,73m²)									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	Xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-

BUN (mg/dl)									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	Xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
BNP									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	Xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
NT-proBNP									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	Xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-

BNP= B-type natriuretic peptide; BUN= blood urea nitrogen; DPP-4= dipeptidyl peptidase-4; HbA1c= Glycated haemoglobin; HDL= high-density lipoprotein; LDL= low-density lipoprotein; Max= Maximum; Min= Minimum; NT= N-terminal; Q1= 1st quartile; Q3= 3rd quartile; Sd= standard deviation; SGLT-2= sodium-glucose cotransporter-2; std=standardized difference.

Table 3. Baseline (12 months prior to index date) summaries for healthcare resource utilization and healthcare cost variables in after-matching cohort in [main/subgroup analyses] comparing the main exposure sub-cohort (empagliflozin/any SGLT-2 inhibitor; separate table for each) and the comparator sub-cohort (any DPP-4 inhibitor).

	Country 1			Country 2			Country 3		
Variable	**Main exposure sub-cohort**	**Comparator sub-cohort**	**Std**	**Main exposure sub-cohort**	**Comparator sub-cohort**	**Std**	**Main exposure sub-cohort**	**Comparator sub-cohort**	**Std**
Number of patients	n	n		n	n		n	n	
HCRU variables									
Combined comorbidity score									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Total N distinct diagnosis codes									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-

Number of different medications									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Any hospitalization									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Any hospitalization within prior 30 days									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Any hospitalization during prior 31-365 days									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Number of hospitalizations									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx

sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Number of in-hospital days									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Number of emergency department visits									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Number of office visits									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-

Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Endocrinologist visit									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Endocrinologist visit (30 days prior									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Endocrinologist visit (31 to 365 days prior									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Number of endocrinologist visits									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-

Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Internal medicine (IM)/family medicine (FM) visits									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
IM/FM visit (30 days prior									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
IM/FM visit (31 to 365 days prior									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Number of IM/FM visits									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-

Cardiologist visit									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Cardiologist visit (30 days prior									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Cardiologist visit (31 to 365 days prior									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Number of cardiologist visits									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Electrocardiogram									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx

No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Number electrocardiograms received									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Use of glucose test strips									
Yes	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
No	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Number of HbA1c tests ordered									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Number of glucose tests ordered									

Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Number of lipid tests ordered									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Number of creatinine tests ordered									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Number of BUN tests ordered									

Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Number of tests for microalbuminuria									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Healthcare cost variables									
The total cost of care									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Inpatient cost									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx

sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Total CV-related inpatient cost									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Total non-CV-related inpatient cost									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Total outpatient cost									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-

Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Total CV-related outpatient cost									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Total non-CV-related outpatient cost									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Total pharmacy cost									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-

Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Total pharmacy cost for antidiabetic medications									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-
Total pharmacy cost for non-antidiabetic medications									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Missing	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-	n (p.pp)	n (p.pp)	-

BUN= blood urea nitrogen; CV= cardiovasclar; DPP-4= dipeptidyl peptidase-4; FM= Family medicine; HbA1c= Glycated haemoglobin; HCRU= healthcare resource utilization; IM= Internal medicine; Max= Maximum; Min= Minimum; Q1= 1st quartile; Q3= 3rd quartile; sd= standard deviation; SGLT-2= sodium-glucose cotransporter-2; std= standardized difference.

Table 4. Baseline (12 months prior to index date) summaries of comorbidities and medications in after-matching cohort in [main/subgroup analyses] comparing the main exposure sub-cohort (empagliflozin/any SGLT-2 inhibitor; separate table for each) and the comparator sub-cohort (any DPP-4 inhibitor).

Variable	Country 1			Country 2			Country 3		
	Main exposure sub-cohort	**Comparator sub-cohort**	**Std**	**Main exposure sub-cohort**	**Comparator sub-cohort**	**Std**	**Main exposure sub-cohort**	**Comparator sub-cohort**	**Std**
Number of patients	n	n	-	n	n	-	n	n	-
Diabetes complications									
Diabetic retinopathy	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Diabetes with other ophthalmic manifestations	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Retinal detachment, vitreous hemorrhage, vitrectomy	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Retinal laser coagulation therapy	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Diabetic neuropathy	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Diabetic nephropathy	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Hypoglycemia	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Hyperglycemia	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Disorders of fluid electrolyte and acid-base balance	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Diabetic ketoacidosis	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Hyperosmolar hyperglycemic nonketotic syndrome (HONK)	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx

Diabetes with peripheral circulatory disorders	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Diabetic foot	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Gangrene	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Lower extremity amputation	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Osteomyelitis	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Skin infections	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Erectile dysfunction	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Diabetes with unspecified complication	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Diabetes mellitus without mention of complications	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Other comorbidites									
Diseases of the circulatory system									
Hypertension	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Hyperlipidemia	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Ischemic heart disease	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Acute MI	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Acute coronary syndrome/unstable angina	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Old MI	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Stable angina	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Coronary atherosclerosis and other forms of chronic ischemic heart disease	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx

Other atherosclerosis	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Any stroke	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Ischemic stroke (with and without mention of cerebral infarction)	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Hemorrhagic stroke	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Other cerebrovascular disease	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Late effects of cerebrovascular disease	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Congestive heart failure (CHF)	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Peripheral vascular disease or surgery	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Atrial fibrillation	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Other cardiac dysrhythmia	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Cardiac conduction disorders	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Other CV disease	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Hypertensive nephropathy	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Hypertension 1 code	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Procedures of the circulatory system									
Previous cardiac procedure	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
History of CABG or PTCA	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Cerebrovascular procedure	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Diseases of the blood and blood-forming organs									

Edema	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Diseases of the digestive system									
Liver disease	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Diseases of the eye and adnexa									
Glaucoma or cataracts	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Diseases of the genitourinary system									
Renal dysfunction (non-diabetic)	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Acute renal disease	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Chronic renal insufficiency	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Chronic renal insufficiency without chronic kidney disease	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Miscellaneous renal insufficiency	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Chronic kidney disease	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Chronic kidney disease stage 1-2	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Chronic kidney disease stage 3-4	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Chronic kidney disease stage 3-6	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Dialysis	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Diseases of the musculoskeletal system and connective tissue									
Osteoarthritis	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx

Other arthritis, arthropathies and musculoskeletal pain	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Dorsopathies	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Osteoporosis	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Diseases of the nervous system									
TIA	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Obstructive sleep apnea	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Sleep disorder	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Diseases of the respiratory system									
COPD	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Asthma	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Pneumonia	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Diseases of the skin and subcutaneous tissue									
Foot ulcer	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Cellulitis or abscess of toe	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Endocrine, nutritional and metabolic diseases									
Hyperlipidemia	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Hyperthyroidism	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Hypothyroidism	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Other disorders of thyroid gland	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Injuries									
Bone Fractures	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx

Falls	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Mental and behavioural disorders									
Depression	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Anxiety	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Dementia	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Delirium	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Psychosis	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Other									
Frailty	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Imaging	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Prior/concomitant use of other antidiabetic drugs*									
N antidiabetic substances at index date									
Mean	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx	xx.xx	xx.xx	x.xx
sd	xx.xx	xx.xx	-	xx.xx	xx.xx	-	xx.xx	xx.xx	-
Median	xx	xx	-	xx	xx	-	xx	xx	-
Q1; Q3	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Min; Max	xx; xx	xx; xx	-	xx; xx	xx; xx	-	xx; xx	xx; xx	-
Naïve new use of antidiabetic drugs	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Initiation of the study drug (empagliflozin/any SGLT-2 inhibitor/any DPP-4 inhibitor) as monotherapy	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx

Dual therapy with metformin (without use of other antidiabetic drugs)	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Concomitant initiation or current use of other antidiabetic drugs	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Past use of other antidiabetic drugs	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Metformin	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Sulfonylureas 2nd generation	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
GLP-1 receptor agonists	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Thiazolidinediones	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Meglitinides	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Insulin	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Alpha-glucosidase inhibitors	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Any use of pramlintide	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Any use of 1st generation sulfonylureas	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Prior use of other drugs									
ACE inhibitor	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
ARB	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Beta-blocker	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Calcium channel blocker	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Thiazides	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Loop diuretics	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx

Other diuretics	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Nitrates	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Other hypertension drugs	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Digoxin	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Valsartan and sacubitril	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Antiarrhythmic drugs	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
COPD or asthma medications	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Statin	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
PCSK-9 inhibitors	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Other lipid-lowering drugs, excluding statins	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Antiplatelet	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Anticoagulants	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Heparin and other low-molecular weight heparins	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
NSAIDs	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Oral corticosteroids	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Bisphosphonates	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Opioids	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Antidepressants	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Antipsychotics	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Anticonvulsants	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Lithium	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx

Benzodiazepines	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Other anxiolytics/hypnotics	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Agents for dementia	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx
Anti- Parkinson agents	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx	n (p.pp)	n (p.pp)	x.xx

ACE= angiotensin-converting-enzyme; ARB= angiotensin II receptor blocker; CABG= coronary artery bypass grafting; CHF= congestive heart failure; COPD= chronic obstructive pulmonary disease; CV= cardiovascular; DPP-4= dipeptidyl peptidase-4; GLP-1= glucagon-like peptide-1; HONK= Hyperosmolar hyperglycemic nonketotic syndrome; MI= myocardial infarction; Min= minimum; Max= maximum; NSAID= nonsteroidal anti-inflammatory drug; PCSK-9= Proprotein convertase subtilisin/kexin type 9 ; PTCA= percutaneous transluminal coronary angioplasty; Q1= 1st quartile; Q3= 3rd quartile; sd= standard deviation; SGLT-2= sodium-glucose cotransporter-2; std= standardized difference; TIA= transient ischemic attack.

* To determine prior, concomitant or current use of other antidiabetic drugs, exactly 12 months prior to index date including the index date is used.

Table 5. Distribution of index drugs by sub-cohort in each country in [main/subgroup analyses] comparing the main exposure sub-cohort (empagliflozin/any SGLT-2 inhibitor; separate table for each) vs comparator sub-cohort (any DPP-4 inhibitor).

	Number of patients		
Variable	**Country 1**	**Country 2**	**Country 3**
SGLT-2 inhibitors	xx	xx	xx
Dapagliflozin	xx	xx	xx
Canagliflozin	xx	xx	xx
Empagliflozin	xx	xx	xx
Ertugliflozin	xx	xx	xx
Ipragliflozin	xx	xx	xx
Dapagliflozin and metformin	xx	xx	xx
Canagliflozin and metformin	xx	xx	xx
Empagliflozin and metformin	xx	xx	xx
Ertugliflozin and metformin	xx	xx	xx
DPP-4 inhibitors	xx	xx	xx
Sitagliptin	xx	xx	xx
Sitagliptin and metformin	xx	xx	xx
Sitagliptin and pioglitazone	xx	xx	xx
Sitagliptin and simvastatin	xx	xx	xx
Vildagliptin	xx	xx	xx
Vildagliptin and metformin	xx	xx	xx
Saxagliptin	xx	xx	xx
Saxagliptin and metformin	xx	xx	xx
Alogliptin	xx	xx	xx
Alogliptin and pioglitazone	xx	xx	xx
Alogliptin and metformin	xx	xx	xx
Linagliptin	xx	xx	xx
Linagliptin and metformin	xx	xx	xx
Gemigliptin	xx	xx	xx
Gemigliptin and rosuvastatin	xx	xx	xx
Gemigliptin and metformin	xx	xx	xx
Evogliptin	xx	xx	xx
Evogliptin and metformin	xx	xx	xx

DPP-4= dipeptidyl peptidase-4; SGLT-2= sodium-glucose cotransporter-2.

Table 6. Summary of [outcome] in [main/subgroup analyses] using [grace period] comparing the main exposure sub-cohort (empagliflozin/any SGLT-2 inhibitor; separate table for each) vs comparator sub-cohort (any DPP-4 inhibitor) with [exposure time] approach [using exposure risk window of 30/14/90 days].

	Country 1		**Country 2**		**Country 3**	
Characteristic	**Main exposure sub-cohort**	**Comparator sub-cohort**	**Main exposure sub-cohort**	**Comparator sub-cohort**	**Main exposure sub-cohort**	**Comparator sub-cohort**
Number of patients	xx	xx	xx	xx	xx	xx
Number of patients with event	xx	xx	xx	xx	xx	xx
Total follow-up time	xx	xx	xx	xx	xx	xx
Number of censored patients due to death	xx	xx	xx	xx	xx	xx
Number of censored patients due to discontinuation or change of index drug*	xx	xx	xx	xx	xx	xx
Number of censored patients due to end of data availability due to other reasons	xx	xx	xx	xx	xx	xx
Number of censored patients due to end of data availability due to end of study period	xx	xx	xx	xx	xx	xx

DPP-4= dipeptidyl peptidase-4; SGLT-2= sodium-glucose cotransporter-2.

*The follow-up time will be censored in occurence of discontinuation of the initial drug use, switch to any other study drug (empagliflozin, any SGLT-2 inhibitor, any DPP-4 inhibitor (including drugs that are marketed locally and are not study drugs in this multi-country studies)), initiation of concomitant use of empagliflozin/SGLT-2 inhibitor and a DPP-4 inhibitor use (including drugs that are marketed locally and are not study drugs in this multi-country study) or drugs within the same class (i.e. two SGLT-2 inhibitors or two DPP-4 inhibitors) either as free or fixed dose combination. So if we know that the index drug use has come to an end or concomitant use has been started, this is the reason for censoring in the AT analysis. This cause of censoring will not be used in ITT analysis.

Table 7. Assessment of possible bias

Country	Covariate availability	Covariate adjustment	Matching success	Data availability for sufficient follow-up time	[redacted]	Drug distribution	Other deviations from master protocol	Total
Denmark								
Finland								
Germany								
Israel								
Japan								
Norway								
South Korea								
Spain								
Sweden								
Taiwan								
the United Kingdom								

Possible values in the table are: high risk, medium risk and low risk.

Table 8. Flowchart numbers

Condition	Country 1	Country 2	Country 3
Number of patients with type 2 diabetes mellitus during MA date to 2018	xx	xx	xx
Number of patients with new initiation of empagliflozin, any SGLT-2 inhibitor or any DPP-4 inhibitor use during study period and identified T2DM	xx	xx	xx
Number of patients after excluding patients aged under 18 years at index date	xx	xx	xx
Number of patients after excluding patients with pre-existing diagnosis of T1DM during the 12 months before the index date	xx	xx	xx
Number of patients after excluding patients with pre-existing diagnosis of secondary diabetes or gestational diabetes in the 12 months prior to the index date.	xx	xx	xx
Number of patients after excluding patients with recorded end-stage renal disease during the 12 months prior to index date	xx	xx	xx
Number of patients after excluding patients who have less than 12 months of available data before the index date and/or no complete drug dispensation/prescription history during this period	xx	xx	xx

Number of patients after excluding patients with missing or ambiguous data on age or gender	xx	xx	xx
Patients initiating empagliflozin	xx	xx	xx
Patients initiating any SGLT-2 inhibitor	xx	xx	xx
Patients initiating any DPP-4 inhibitor	xx	xx	xx

DPP-4= dipeptidyl peptidase-4;MA= marketing authorization; SGLT-2= sodium-glucose cotransporter-2;T1DM= type1 diabetes mellitus; T2DM= type 2 diabetes mellitus.

Table 9. Healthcare resource utilization outcomes in [main/subgroup analyses] comparing the main exposure sub-cohort (empagliflozin) vs comparator sub-cohort (any DPP-4 inhibitor).

		Country 1		Country 2		Country 3	
Outcome		**Main exposure sub-cohort**	**Comparator sub-cohort**	**Main exposure sub-cohort**	**Comparator sub-cohort**	**Main exposure sub-cohort**	**Comparator sub-cohort**
	Number of patients	**xx**	**xx**	**xx**	**xx**	**Xx**	**xx**
Outpatient healthcare visits excluding emergency room visits	Total number	xx	xx	xx	xx	Xx	xx
	Person-years	xx	xx	xx	xx	Xx	xx
	Incident rate	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Per member per year	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Emergency room visits	Total number	xx	xx	xx	xx	Xx	xx
	Person-years	xx	xx	xx	xx	Xx	xx
	Incident rate	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Per member per year	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
All caused hospital admissions	Total number	xx	xx	xx	xx	Xx	xx
	Person-years	xx	xx	xx	xx	Xx	xx
	Incident rate	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Per member per year	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Pharmacy dispensations/other records of drug use	Total number	xx	xx	xx	xx	Xx	xx
	Person-years	xx	xx	xx	xx	Xx	xx
	Incident rate	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
First inpatient stay	Total number	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Person-years	xx	xx	xx	xx	Xx	xx
	Incident rate	xx	xx	xx	xx	Xx	xx

DPP-4= dipeptidyl peptidase-4.

Table 10. Summary of inpatient days in [main/subgroup analyses] comparing the main exposure sub-cohort (empagliflozin) vs comparator sub-cohort (any DPP-4 inhibitor).

	Country 1		Country 2		Country 3	
Characteristic	**Main exposure sub-cohort**	**Comparator sub-cohort**	**Main exposure sub-cohort**	**Comparator sub-cohort**	**Main exposure sub-cohort**	**Comparator sub-cohort**
Number of patients	xx	xx	xx	xx	xx	xx
Total number of inpatient days	xx	xx	xx	xx	xx	xx
Total follow-up time	xx	xx	xx	xx	xx	xx
Mean of % of fup	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
sd of % of fup	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median of % of fup	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Q1; Q3 of % of fup	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx
$q_{0.95}$; $q_{0.99}$ of % of fup	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx
Min; Max of % of fup	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx
Inpatient days per member per year	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

DPP-4= dipeptidyl peptidase-4; fup= follow-up; max= maximum; min= minimum; Q1= 1st quartile; Q3= 3rd quartile; $q_{0.95}$=0.95-quantile; $q_{0.99}$=0.99-quantile; sd= standard deviation.

Table 11. Summary of average length of stay (in days) in [main/subgroup analyses] comparing the main exposure sub-cohort (empagliflozin) vs comparator sub-cohort (any DPP-4 inhibitor) within patients with hospital admissions.

	Country 1		Country 2		Country 3	
Characteristic	**Main exposure sub-cohort**	**Comparator sub-cohort**	**Main exposure sub-cohort**	**Comparator sub-cohort**	**Main exposure sub-cohort**	**Comparator sub-cohort**
Number of patients	xx	xx	xx	xx	xx	xx
Number of patients with hospital admissions	xx	xx	xx	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
sd	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Q1; Q3	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx
Min; Max	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx	xx.xx; xx.xx

DPP-4= dipeptidyl peptidase-4; max= maximum; min= minimum; Q1= 1st quartile; Q3= 3rd quartile; sd= standard deviation.

Table 12. Time to event analysis results of first inpatient stay (hospital admission) in [main/subgroup analyses] comparing the main exposure sub-cohort (empagliflozin) vs comparator sub-cohort (any DPP-4 inhibitor).

Country	Hazard ratio	SE	Lower CI	Upper CI
Country 1	xx.xx	xx.xx	xx.xx	xx.xx
Country 2	xx.xx	xx.xx	xx.xx	xx.xx
Country 3	xx.xx	xx.xx	xx.xx	xx.xx
Country 4	xx.xx	xx.xx	xx.xx	xx.xx
Country 5	xx.xx	xx.xx	xx.xx	xx.xx
Country 6	xx.xx	xx.xx	xx.xx	xx.xx
Country 7	xx.xx	xx.xx	xx.xx	xx.xx
Country 8	xx.xx	xx.xx	xx.xx	xx.xx
Country 9	xx.xx	xx.xx	xx.xx	xx.xx
Country 10	xx.xx	xx.xx	xx.xx	xx.xx
Country 11	xx.xx	xx.xx	xx.xx	xx.xx

DPP-4= dipeptidyl peptidase-4; CI= confidence interval; SE= standard error.

Table 13. Analysis results of [healthcare resource utilization/healthcare cost] outcomes in [main/subgroup analyses] comparing the main exposure sub-cohort (empagliflozin) vs comparator sub-cohort (any DPP-4 inhibitor).

	All-caused hospital admissions		**Outpatient healthcare visits excluding emergency room visits**		**Emergency room visits**		**Number of dispensations/other records of drug use**	
Outcome	**Rate ratio**	**CI**	**Rate ratio**	**CI**	**Rate ratio**	**CI**	**Rate ratio**	**CI**
Country 1	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)
Country 2	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)
Country 3	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)
Country 4	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)
Country 5	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)
Country 6	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)
Country 7	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)
Country 8	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)
Country 9	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)
Country 10	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)
Country 11	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)	xx.xx	(xx.xx ; xx.xx)

CI= confidence interval; DPP-4= dipeptidyl peptidase-4.

10.3 ALL PLANNED ANALYSES

Table 14. List of all planned analyses.

Analysis	Outcome	main exposure sub-cohort	subgroups	exp. type	grace period	risk window	Countries	template
meta-analysis	HHF	empagliflozin, SGLT-2	Main cohort	AT	100%, 30 days, 90 days	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	ACM	empagliflozin, SGLT-2	Main cohort	AT	100%, 30 days, 90 days	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	HHF+ACM	empagliflozin, SGLT-2	Main cohort	AT	100%, 30 days, 90 days	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**

meta-analysis	MI	empagliflozin, SGLT-2	Main cohort	AT	100%, 30 days, 90 days	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Stroke	empagliflozin, SGLT-2	Main cohort	AT	100%, 30 days, 90 days	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	MI+Stroke+ ACM	empagliflozin, SGLT-2	Main cohort	AT	100%, 30 days, 90 days	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	HHF	empagliflozin, SGLT-2	Main cohort	ITT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunde**

								n werden.
meta-analysis	ACM	empagliflozin, SGLT-2	Main cohort	ITT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	HHF+ACM	empagliflozin, SGLT-2	Main cohort	ITT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	MI	empagliflozin, SGLT-2	Main cohort	ITT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Stroke	empagliflozin, SGLT-2	Main cohort	ITT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht**

								gefunden werden.
meta-analysis	MI+Stroke+ ACM	empagliflozin, SGLT-2	Main cohort	ITT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	HHF	empagliflozin	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg, sitagliptin	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	ACM	empagliflozin	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg, sitagliptin	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	HHF+ACM	empagliflozin	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg, sitagliptin	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte**

								nicht gefunden werden.
meta-analysis	MI	empagliflozin	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg, sitagliptin	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Stroke	empagliflozin	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg, sitagliptin	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	MI+Stroke+ ACM	empagliflozin	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg, sitagliptin	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	HHF	SGLT-2	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Figure 3**Fehler! Verweisquelle**

								konnte nicht gefunden werden.
meta-analysis	ACM	SGLT-2	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	HHF+ACM	SGLT-2	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	MI	SGLT-2	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Stroke	SGLT-2	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Figure 3**Fehler! Verweis**

								quelle konnte nicht gefunden werden.
meta-analysis	MI+Stroke+ ACM	SGLT-2	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Figure 3**Fehler! Verweis quelle konnte nicht gefunden werden.**
meta-analysis	CVM	empagliflozin, SGLT-2	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Figure 3**Fehler! Verweis quelle konnte nicht gefunden werden.**
meta-analysis	HHF+CVM	empagliflozin, SGLT-2	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Figure 3**Fehler! Verweis quelle konnte nicht gefunden werden.**
meta-analysis	MACE	empagliflozin, SGLT-2	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Figure 3**Fehler!**

								Verweisquelle konnte nicht gefunden werden.
meta-analysis	Coronary revasc.	empagliflozin, SGLT-2	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	ESRD	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	eGFR decline (a)	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**

meta-analysis	eGFR decline (b)*	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Prog. to micro-/macroalb.	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	eGFR + Albumin.	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	ESRD	SGLT-2	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunde**

								n werden.
meta-analysis	eGFR decline (a)	SGLT-2	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	eGFR decline (b)*	SGLT-2	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Prog. to micro-/macroalb.	SGLT-2	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	eGFR + Albumin.	SGLT-2	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Figure 3**Fehler! Verweisquelle konnte nicht**

								gefunden werden.
meta-analysis	Bone fractures	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	30 days, 14 days, 90 days	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Diabetic ketoacidosis	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	30 days, 14 days, 90 days	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Severe hypoglycemia	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	30 days, 14 days, 90 days	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Lower-limb amputation	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	30 days, 14 days, 90 days	All	Figure 3**Fehler! Verweisquelle konnte**

								nicht gefunden werden.
meta-analysis	Acute kidney injury	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	30 days, 14 days, 90 days	All	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
Baseline descriptive	-	empagliflozin	Main cohort, additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg, sitagliptin	-	-	-	All	Table 2 Table 3 Table 4
Baseline descriptive	-	SGLT-2	Main cohort, additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+,	-	-	-	All	Table 2 Table 3 Table 4
Baseline descriptive	eGFR decline (a)	empagliflozin, SGLT-2	Main cohort	-	-	-	All	Table 2 Table 3 Table 4
Baseline descriptive	eGFR decline (b)*	empagliflozin, SGLT-2	Main cohort	-	-	-	All	Table 2 Table 3 Table 4
Baseline descriptive	Prog. to micro-/macroalb.	empagliflozin, SGLT-2	Main cohort	-	-	-	All	Table 2 Table 3 Table 4
Baseline descriptive	eGFR + Albumin.	empagliflozin, SGLT-2	Main cohort	-	-	-	All	Table 2 Table 3 Table 4

Index drug distribution	-	empagliflozin	Main cohort, additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg, sitagliptin	-	-	-	All	Table 5
Index drug distribution	-	SGLT-2	Main cohort, additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	-	-	-	All	Table 5
Index drug distribution	eGFR decline (a)	empagliflozin, SGLT-2	Main cohort	-	-	-	All	Table 5
Index drug distribution	eGFR decline (b)*	empagliflozin, SGLT-2	Main cohort	-	-	-	All	Table 5
Index drug distribution	Prog. to micro-/macroalb.	empagliflozin, SGLT-2	Main cohort	-	-	-	All	Table 5
Index drug distribution	eGFR + Albumin.	empagliflozin, SGLT-2	Main cohort	-	-	-	All	Table 5
Events descriptive	HHF	empagliflozin, SGLT-2	Main cohort	AT	100%, 30 days, 90 days	-	All	Table 6
Events descriptive	ACM	empagliflozin, SGLT-2	Main cohort	AT	100%, 30 days, 90 days	-	All	Table 6
Events descriptive	HHF+ACM	empagliflozin, SGLT-2	Main cohort	AT	100%, 30 days, 90 days	-	All	Table 6
Events descriptive	MI	empagliflozin, SGLT-2	Main cohort	AT	100%, 30 days, 90 days	-	All	Table 6
Events descriptive	Stroke	empagliflozin, SGLT-2	Main cohort	AT	100%, 30 days, 90 days	-	All	Table 6

Events descriptive	MI+Stroke+ ACM	empagliflozin, SGLT-2	Main cohort	AT	100%, 30 days, 90 days	-	All	Table 6
Events descriptive	HHF	empagliflozin, SGLT-2	Main cohort	ITT	100%,	-	All	Table 6
Events descriptive	ACM	empagliflozin, SGLT-2	Main cohort	ITT	100%	-	All	Table 6
Events descriptive	HHF+ACM	empagliflozin, SGLT-2	Main cohort	ITT	100%	-	All	Table 6
Events descriptive	MI	empagliflozin, SGLT-2	Main cohort	ITT	100%	-	All	Table 6
Events descriptive	Stroke	empagliflozin, SGLT-2	Main cohort	ITT	100%	-	All	Table 6
Events descriptive	MI+Stroke+ ACM	empagliflozin, SGLT-2	Main cohort	ITT	100%	-	All	Table 6
Events descriptive	HHF	empagliflozin	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg, sitagliptin	AT	100%	-	All	Table 6
Events descriptive	ACM	empagliflozin	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg, sitagliptin	AT	100%	-	All	Table 6
Events descriptive	HHF+ACM	empagliflozin	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg, sitagliptin	AT	100%	-	All	Table 6
Events descriptive	MI	empagliflozin	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg, sitagliptin	AT	100%	-	All	Table 6
Events descriptive	Stroke	empagliflozin	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg, sitagliptin	AT	100%	-	All	Table 6

Events descriptive	MI+Stroke+ ACM	empagliflozin	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg, sitagliptin	AT	100%	-	All	Table 6
Events descriptive	HHF	SGLT-2	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Table 6
Events descriptive	ACM	SGLT-2	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Table 6
Events descriptive	HHF+ACM	SGLT-2	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Table 6
Events descriptive	MI	SGLT-2	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Table 6
Events descriptive	Stroke	SGLT-2	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Table 6
Events descriptive	MI+Stroke+ ACM	SGLT-2	Additional exclusion criteria, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Table 6
Events descriptive	CVM	empagliflozin, SGLT-2	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Table 6
Events descriptive	HHF+CVM	empagliflozin, SGLT-2	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Table 6
Events descriptive	MACE	empagliflozin, SGLT-2	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Table 6
Events descriptive	Coronary revasc.	empagliflozin, SGLT-2	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Table 6
Events descriptive	ESRD	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg	AT	100%	-	All	Table 6
Events descriptive	eGFR decline (a)	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg	AT	100%	-	All	Table 6
Events descriptive	Prog. to micro-/macroalb.	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg	AT	100%	-	All	Table 6

Events descriptive	EGFR + Albumin.	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+, empa10mg, empa25mg	AT	100%	-	All	Table 6
Events descriptive	ESRD	SGLT-2	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Table 6
Events descriptive	eGFR decline (a)	SGLT-2	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Table 6
Events descriptive	Prog. to micro-/macroalb.	SGLT-2	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Table 6
Events descriptive	EGFR + Albumin.	SGLT-2	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	-	All	Table 6
Events descriptive	Bone fractures	empagliflozin	Main cohort	AT	100%	30 days, 14 days, 90 days	All	Table 6
Events descriptive	Diabetic ketoacidosis	empagliflozin	Main cohort	AT	100%	30 days, 14 days, 90 days	All	Table 6
Events descriptive	Severe hypoglycemia	empagliflozin	Main cohort	AT	100%	30 days, 14 days, 90 days	All	Table 6
Events descriptive	Lower-limb amputation	empagliflozin	Main cohort	AT	100%	30 days, 14 days, 90 days	All	Table 6
Events descriptive	Acute kidney injury	empagliflozin	Main cohort	AT	100%	30 days, 14 days, 90 days	All	Table 6
Events descriptive	Bone fractures	empagliflozin	CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	30 days	All	Table 6
Events descriptive	Diabetic ketoacidosis	empagliflozin	CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	30 days	All	Table 6

Events descriptive	Severe hypoglycemia	empagliflozin	CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	30 days	All	Table 6
Events descriptive	Lower-limb amputation	empagliflozin	CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	30 days	All	Table 6
Events descriptive	Acute kidney injury	empagliflozin	CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-, Metformin(12M)+	AT	100%	30 days	All	Table 6
HCRU descriptive	Outpatient healthcare visits excluding emergency department visits	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	All	Table 9
HCRU descriptive	Emergency room visits	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	All	Table 9
HCRU descriptive	All-caused hospital admissions	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	All	Table 9
HCRU descriptive	Pharmacy dispensations/prescriptions	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	All	Table 9
HCRU descriptive	First inpatient stay	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	All	Table 9
HCRU descriptive	Number of inpatient days	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	All	Table 10

HCRU descriptive	Average length of stay	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	All	Table 11
Compari-son of the results	First inpatient stay	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	All	Table 12
Compari-son of the results	Number of all-caused hospital admissions	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	All	Table 13
Compari-son of the results	Number of outpatient visits excluding emergency room visits	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	All	Table 13
Compari-son of the results	Number emergency room visits	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	All	Table 13
Compari-son of the results	Number of dispensations/prescriptions	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	All	Table 13
Compari-son of the results	Costs of inpatient visits	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	All	Table 13
Compari-son of the results	Costs of outpatient visits	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	All	Table 13
Comparis on of the results	Costs of dispensation	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	All	Table 13

	s/prescriptions							
Comparison of the results	Total costs	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	All	Table 13
Flowchart	-	-	Main cohort	-	-	-	All	Table 8
meta-analysis	HHF	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Nordics	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	ACM	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Nordics	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	HHF+ACM	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Nordics	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**

meta-analysis	MI	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Nordics	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Stroke	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Nordics	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	MI+Stroke+ ACM	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Nordics	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	First inpatient stay	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	Nordics	Figure 3**Fehler! Verweisquelle konnte nicht gefunde**

								n werden.
meta-analysis	Number of all-caused hospital admissions	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	Nordics	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Number of outpatient visits excluding emergency room visits	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	Nordics	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Number emergency room visits	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	Nordics	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Number of dispensations/prescriptions	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	Nordics	Figure 3**Fehler! Verweisquelle konnte nicht**

								gefunden werden.
meta-analysis	HHF	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Asian	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	ACM	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Asian	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	HHF+ACM	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Asian	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	MI	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Asian	Figure 3**Fehler! Verweisquelle konnte**

								nicht gefunden werden.
meta-analysis	Stroke	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Asian	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	MI+Stroke+ ACM	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Asian	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	First inpatient stay	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	Asian	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Number of all-caused hospital admissions	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	Asian	Figure 3**Fehler! Verweisquelle**

								konnte nicht gefunden werden.
meta-analysis	Number of outpatient visits excluding emergency room visits	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	Asian	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Number emergency room visits	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	Asian	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Number of dispensations/prescriptions	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	Asian	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	HHF	empagliflozin, SGLT-2	Main cohort	AT	100%	-	European countries	Figure 3**Fehler! Verweis**

								quelle konnte nicht gefunden werden.
meta-analysis	ACM	empagliflozin, SGLT-2	Main cohort	AT	100%	-	European countries	Figure 3**Fehler! Verweis quelle konnte nicht gefunden werden.**
meta-analysis	HHF+ACM	empagliflozin, SGLT-2	Main cohort	AT	100%	-	European countries	Figure 3**Fehler! Verweis quelle konnte nicht gefunden werden.**
meta-analysis	MI	empagliflozin, SGLT-2	Main cohort	AT	100%	-	European countries	Figure 3**Fehler! Verweis quelle konnte nicht gefunden werden.**
meta-analysis	Stroke	empagliflozin, SGLT-2	Main cohort	AT	100%	-	European countries	Figure 3**Fehler!**

								Verweis quelle konnte nicht gefunden werden.
meta-analysis	MI+Stroke+ ACM	empagliflozin, SGLT-2	Main cohort	AT	100%	-	European countries	Figure 3**Fehler! Verweis quelle konnte nicht gefunden werden.**
meta-analysis	First inpatient stay	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	European countries	Figure 3**Fehler! Verweis quelle konnte nicht gefunden werden.**
meta-analysis	Number of all-caused hospital admissions	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	European countries	Figure 3**Fehler! Verweis quelle konnte nicht gefunden werden.**

meta-analysis	Number of outpatient visits excluding emergency room visits	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	European countries	Figure 3**Fehler! Verweis quelle konnte nicht gefunden werden.**
meta-analysis	Number emergency room visits	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	European countries	Figure 3**Fehler! Verweis quelle konnte nicht gefunden werden.**
meta-analysis	Number of dispensations/prescriptions	empagliflozin	Main cohort, CHF(12M)+, CHF(12M)-, CV(12M)+, CV(12M)-, CV/CHF(60D)+, CV/CHF(60D)-	AT	100%	-	European countries	Figure 3**Fehler! Verweis quelle konnte nicht gefunden werden.**
meta-analysis	HHF	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Asian countries + selected European countries	Figure 3**Fehler! Verweis quelle konnte nicht gefunde**

								n werden.
meta-analysis	ACM	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Asian countries + selected European countries	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	HHF+ACM	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Asian countries + selected European countries	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	MI	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Asian countries + selected European countries	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Stroke	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Asian countries + selected European countries	Figure 3**Fehler! Verweisquelle konnte nicht**

								gefunden werden.
meta-analysis	MI+Stroke+ ACM	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Asian countries + selected European countries	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	HHF	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Lab data available	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	ACM	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Lab data available	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	HHF+ACM	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Lab data available	Figure 3**Fehler! Verweisquelle konnte**

								nicht gefunden werden.
meta-analysis	MI	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Lab data available	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	Stroke	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Lab data available	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**
meta-analysis	MI+Stroke+ ACM	empagliflozin, SGLT-2	Main cohort	AT	100%	-	Lab data available	Figure 3**Fehler! Verweisquelle konnte nicht gefunden werden.**

12M= 12 months prior index date; 60D= 60 days prior index date; ACM= all-cause mortality; AT= as treated; CHF= congestive heart failure; CV= cardiovascular; CVM= cardiovascular mortality; eGFR= estimated glomerular filtration rate; eGFR+Albumin.= Composite outcome of eGFR decline (a) and progression to micro-/macroalbuminuria; empa10mg= start dose of empagliflozin 10 mg; empa25mg= start dose of empagliflozin 25mg; ESRD= end-stage renal disease; HHF=

hospitalization for heart failure; ITT= intention to treat; MACE= major adverse cardiovascular event; macroalb.= macroalbuminuria; Prog.= Progression; MI= myocardial infarction; SGLT-2= sodium-glycose cotransporter-2; revasc.= revascularisation.

* Analysis of the outcome EGFR decline (b) will be carried out in different time intervals (overall, week 5 – 12 months, 13 months – 24 months).

11 HISTORY TABLE

Version No.	Date (dd Mmm yyyy)	Author	Sections changed	Brief description of change
2.0	22 NOV 2019	[redacted]	Multiple	New renal and safety outcomes included.
2.0	22 NOV 2019		6.1, 10.2, 10.3	Emergency room visits will be analyzed as a separate outcome from outpatient visits in HCRU and cost analyses.
2.0	22 NOV 2019		7.1	Exposure section clarified.
2.0	22 NOV 2019		7.3, 7.4	Update of the inclusion/exclusion criteria for consistency with the protocol amendment.
2.0	22 NOV 2019		7.3, 8.7, 10.3	Safety outcomes, HCRU and cost of care outcomes will be analyzed exclusively for empagliflozin as the exposure group and DPP-4 inhibitors as the comparison group.
2.0	22 NOV 2019		7.4, 10.3	Metformin (12M)+ subgroup added to all secondary effectiveness and safety outcomes.
2.0	22 NOV 2019		7.4, 10.3	Metformin only (12M)+ subgroup was removed from the analyses
2.0	22 NOV 2019		7.4	Subgroup section divided into 2 parts to have local and global level subgroups described separately.
2.0	22 NOV 2019		7.6	Study time-windows clarified.
2.0	22 NOV 2019		7.4.2, 8.7, 10.3	Asian + selected European countries meta-analysis added
2.0	22 NOV 2019		8.5.2, 10.3	Meta-analysis of HCRU outcomes in countries with comparable healthcare systems added
2.0	22 NOV 2019		10.2, 10.3	Average length of stay added as HCRU outcome
2.0	22 NOV 2019		10.2	HCRU outcomes will be presented per member per year instead of per member per month
2.0	22 NOV 2019		Multiple	Description of possible data of drug usage made more general.
2.0	22 NOV 2019		Multiple	Minor changes to make SAP consistent with the updates.