Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

Document Number:	c10612984-02
BI Study Number:	1245.122
BI Investigational Product(s):	Jardiance® (empagliflozin)
Title:	Characteristics of patients initiating empagliflozin or other non-insulin glucose lowering drugs in the United Kingdom
Protocol version identifier:	2.0
Date of last version of protocol:	13 Jun 2016.
PASS:	Yes
EU PAS register number:	Study not registered.
Active substance:	Empagliflozin (ATC code A10BX12)
Medicinal product:	Jardiance
Product reference:	EMEA/H/C/002677
Procedure number:	Not applicable.
Joint PASS:	No
Research question and objectives:	The primary objective of this study is to describe and compare the general characteristics of patients with a recorded diagnosis of type 2 diabetes mellitus (T2DM) starting empagliflozin in the United Kingdom (UK) to the characteristics of patients with a recorded diagnosis of T2DM initiating other sodium glucose cotransporter 2 (SGLT-2) inhibitors or other non-insulin glucose lowering drugs (GLDs). The secondary objective of the study is to assess the extent of off-label use by identifying the proportion and describing the characteristics of patients initiating empagliflozin who do not have a recorded diagnosis for T2DM compared to patients without a recorded diagnosis for T2DM initiating other SGLT-2 inhibitors or other non-insulin GLDs.
Country(-ies) of study:	United Kingdom

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EU-QPPV:	[redacted]
Signature of EU-QPPV:	The signature of the EU-QPPV is provided electronically
Date:	11 August 2016

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2. LIST OF ABBREVIATIONS

ACEi	Angiotensin Converting Enzyme Inhibitors
AE	Adverse Event
AG	Alpha-Glucosidase
ARB	Angiotensin II receptor blockers
ASD	Absolute standardized differences
BI	Boehringer Ingelheim International GmbH
BMI	Body mass index
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DPP-4	Dipeptidyl peptidase-4
DUS	Drug utilization study
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GLD	Glucose lowering drug
GLP-1	Glucagon-like peptide-1
CPRD	Clinical Practice Research Datalink
IRB	Institutional Review Board
ISAC	Independent Scientific Advisory Committee
IQR	interquartile range
GD	Gestational diabetes
LADA	Latent autoimmune diabetes of adults
LMWH	Low molecular weight heparins
MI	Myocardial infarction
MODY	Maturity onset diabetes of the young
PCO	Polycystic ovary syndrome
PS	Propensity score
PSD	Program specification document
RMP	Risk management plan
SAE	Serious Adverse Event
SGLT-2	Sodium glucose cotransporter 2
SOP	Standard operating procedures
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TIA	Transient Ischemic Attack
UK	United Kingdom
UDM	Unspecified diabetes mellitus
UTS	Up to standard

3. RESPONSIBLE PARTIES

The study investigators (Global Epidemiology) at Boehringer Ingelheim International GmbH (BI) are responsible for the design and conduct of the study. The study protocol has been written following the Code of Conduct by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) [R15-4870]. The investigators are responsible for conducting the study in a manner that meets regulatory standards. The study shall be conducted as described in the approved protocol. All revisions to the protocol will be properly documented as protocol amendments.
BI (the financial sponsor of this study) is responsible for submitting the study report to the European Medicines Agency (EMA) (called 'the agency').

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Jardiance			
Name of active ingredient: A10BX12 Empagliflozin			
Protocol date: 13 June 2016	**Study number:** 1245.122	**Version/Revision:** 2.0	**Version/Revision date:** 11 August 2016
Title of study:	Characteristics of patients initiating empagliflozin or other non-insulin glucose lowering drugs in the United Kingdom		
Rationale and background:	Empagliflozin, a sodium glucose cotransporter 2 (SGLT-2) inhibitor, was launched in the United Kingdom (UK) in August 2014. It can be expected that patients initiating empagliflozin may differ in their characteristics from patients initiating other glucose lowering drugs (GLDs) that have been on the market longer (e.g. patients may have poorer glucose control). Therefore, the proposed study aims to characterize patients with T2DM in the UK initiating empagliflozin in terms of baseline characteristics, concomitant medications, and comorbidities compared to patients with T2DM initiating other SGLT-2 inhibitors or other non-insulin GLDs. Due to the mode of action, some patients taking empagliflozin have experienced weight loss in clinical trials. A theoretical possibility exists that empagliflozin may be used by patients without T2DM. Therefore, this study also aims to assess the potential off-label use of empagliflozin compared to other non-insulin GLDs.		
Research question and objectives:	The primary objective of this study is to describe and compare the baseline characteristics of patients with a recorded diagnosis of T2DM in the UK initiating empagliflozin to the characteristics of other non-insulin GLD initiators. The secondary objective of the study is to assess the extent of off-label use by identifying the proportion and describing the baseline characteristics of patients initiating empagliflozin who do not have a recorded diagnosis of T2DM compared to patients without a recorded diagnosis of T2DM initiating other non-insulin GLDs.		
Study design:	A cross-sectional assessment of patients initiating a non-insulin GLD in the UK during the study period (01 August 2014 – 01 September 2015) will be conducted.		

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Protocol date: 13 June 2016	**Study number:** 1245.122	**Version/Revision:** 2.0	**Version/Revision date:** 11 August 2016
Population:	The study will include all eligible individuals in the UK Clinical Practice Research Datalink (CPRD) who have initiated empagliflozin, other SGLT-2 inhibitors, or other commonly used non-insulin GLDs (metformin, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists) from 01 August 2014 through 01 September 2015. Eligible patients will be included if they have at least 12 months of continuous up-to-standard (UTS) registration in the CPRD prior to the index date. The index date will be defined as the date on which each identified new user receives the index prescription. The index prescription will be the first prescription for empagliflozin, other SGLT2 inhibitors, or non-insulin GLDs during the study period. Index prescriptions of the study drugs include the single study drugs or fixed-dose combination (FDC) with metformin of the study drugs when available. To avoid the inclusion of prevalent users, patients will be required to have no exposure to any other medications in the class of interest during the 12 months pre-index period. To study the potential off-label use the study population will be categorized based on the recorded diabetes diagnosis read codes into the following categories: – T2DM (probable/possible/likely) – Type 1 diabetes mellitus (T1DM) (probable/possible/likely) – Unspecified diabetes mellitus (UDM) – Other types of diabetes including: • Maturity onset diabetes of the young (MODY) • Latent autoimmune diabetes of adults (LADA) • Secondary diabetes – Mixed codes of diabetes (patients who had a combination of different diabetes codes (T1DM or T2DM or MODY or LADA, and secondary diabetes) – Gestational diabetes (GD), and pregnant or breast-feeding women with or without any recorded diabetes code – Patients without any diabetes diagnosis codes		

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	All the above categories will be stratified into paediatrics (<18 years ofage) and adults (≥18 years of age).		
Variables:	Exposures (index drugs): – Empagliflozin (and fixed-dose combinations with metformin) – Other SGLT2 inhibitors: dapagliflozin, canagliflozin (and fixed-dose combinations of these drugs with metformin) – Other commonly used non-insulin GLDs (and fixed-dose combinations of these drugs with metformin), including: • Metformin • Sulfonylureas • DPP-4 inhibitors • GLP-1agonists Outcomes: The primary study outcome is to describe and compare the baseline characteristics of patients with a recorded diagnosis of T2DM in the UK initiating empagliflozin to the characteristics of other non-insulin GLD initiators. The secondary outcome of the study is to assess the extent of off-label use by identifying the proportion and describing the baseline characteristics of patients initiating empagliflozin who do not have a recorded diagnosis of T2DM compared to patients without a recorded diagnosis of T2DM initiating other non-insulin GLDs. The following baseline characteristics will be identified (Annex 5): – Demographics – Life style factors – Laboratory tests – Comorbidities – Concomitant medications		

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Data sources:	The UK CPRD is the data source for the present study. In the UK, nearly all residents are registered in a general medical practice that uses electronic medical records. The CPRD contains diagnostic and prescribing information recorded by general practitioners as part of their routine clinical practice in the UK. The database currently contains data for over 13.2 million patients with research-quality data from 680 UK practices; 5.69 million of these patients are active (still registered with a general practice that is contributing data to the CPRD). Patients registered are representative of the whole UK population in terms of age and sex [R16-1231].		
Study size:	The study size will be driven by the uptake of empagliflozin following its approval and launch for the treatment of T2DM in the UK. A feasibility assessment, performed using CPRD data through 01 September 2015, identified 169 patients treated with empagliflozin. The precision of proportion estimates (e.g. prevalence) is a function of the proportion and the number of patients contributing to the proportion (standard error = square root[p(1-p)/n]). Therefore the precision for a prevalence estimate of 10% or 20% is less 5% even for the sample size that will likely be present in this study. For continuous measures, the precision depends on the number of subjects on whom the estimate is made and the variability of the measures (standard error = square root[standard deviation^2/n]). Therefore the precision is sufficiently high for all continuous parameters.		
Data analysis:	The analysis will be descriptive at baseline. Baseline patient characteristics will be tabulated for different exposure groups (empagliflozin, other SGLT-2 inhibitors, and other non-insulin GLDs) and different baseline statuses of diabetes codes (T2DM, T1DM, UDM, other types of diabetes, mixed diagnosis codes, gestational diabetes and breast feeding women, paediatrics, and patients without any diabetes diagnosis codes). All the above categories will be stratified into paediatrics (<18 years of age) and adults (≥18 years of age).		

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	Results will be presented as means, standard deviations, medians, minimum, and maximum and interquartile range (IQR) for continuous variables, and as counts and percentages for categorical variables. Analyses will be conducted in unmatched cohorts. Differences between empagliflozin and each of the other exposure groups will be assessed using absolute standardized differences (ASD), where an ASD of at least 10% will be considered a meaningful difference [R13-3590, R16-1228, R16-1227, R16-1709]. Analyses stratified on patterns of initiation (monotherapy or combination therapy) and naïve versus non-naïve new use will also be conducted. Patients with no use of any glucose lowering medicine (including insulin) in the prior 6 months will be defined as treatment naïve patients. The prevalence (with 95% confidence intervals (CIs)) of potential off-label use among new users of empagliflozin will be calculated and compared with the prevalence of off-label use of other index prescriptions.		
Milestones:	Start of analysis – Q3 2016 End of analysis – Q3 2016 First draft report – Q3 2016 Final study report: Q4 2016		

5. AMENDMENTS AND UPDATES

Protocol version 2.0 is an amendment of version 1.

Version Number	Date	Section of study protocol	Amendment or update	Reason
2.0	11 August 2016	2. List of abbreviations	ISAC was added to the list of abbreviations.	It was missing in the first version.
2.0	11 August 2016	9.3.2. Outcomes, Table 1	LADA was added to Table 1 (definition of secondary diabetes).	It was missing in the first version.
2.0	11 August 2016	9.3.2. Outcomes, Table 1	"Other DM types" was added to Table 1.	It was missing in the first version.
2.0	11 August 2016	9.7.1. Main analysis	"Following recommendation of CPRD Independent Scientific Advisory Committee (ISAC), when reporting the data, CPRD policy is that no cell should contain <5 events" was added.	Following ISAC approval, this section had to be updated.
2.0	11 August 2016	Annex 2	ENCEPP check list was updated.	To update the ENCEPP checklist.

2.0	11 August 2016	Annex 3.	Glymidine sodium with ATC code of A10BC01 was added to Sulphonylureas category with ATC code of A10BB.	To complete the list of Sulphonylureas.
2.0	11 August 2016	Annex 3.	Albiglutide (ATC code A10BX13) was removed from the Glucagon-like peptide-1 (GLP1) agonists category.	This product was launched only early 2016 and therefore it is not coded in CPRD during our study period.
2.0	11 August 2016	Annex 3.	Dulaglutide (ATC code A10BX14) was added to the Glucagon-like peptide-1 (GLP1) agonists category.	This product was in the UK CPRD during our study period.
2.0	11 August 2016	Annex 4.	Annex 4 was updated and following read codes were added: 661M400, 9m02.00, 9m03.00, 9m0B.00, 9NJy.00, C108F12, C109911, C109B12, C10E011, C10E612, C10EQ11, C10FH11, C10P011, K081000, L180700, ZC2C911	These codes were missing in version 1.

2.0	11 August 2016	Annex 5.	Flutter was added.	It was missing in the first version.
2.0	11 August 2016	Annex 5.	Transient Ischemic Attack (TIA) and stroke were merged in one group.	Using harmonized approach across different studies.
2.0	11 August 2016	Annex 5.	Pyelonephritis and urosepsis (UTI following sepsis within 1 week) were added and genital infections was removed.	A more sophisticated approach was developed during code list preparation to reflect different disease stages/severity.
2.0	11 August 2016	Annex 5.	Renal dysfunction, chronic renal insufficiency, And pyelonephritis/infections of kidney were removed and chronic kidney disease category was added.	A more sophisticated approach was developed during code list preparation to reflect different disease stages/severity.
2.0	11 August 2016	Annex 5.	Order of other non-diabetes medications was changed.	Re-ordering of co-medications (mainly oriented by British National Formulary (BNF) chapters).

6. MILESTONES

Milestone	Planned Date
Protocol endorsed by the ISAC committee	Q3 2016
Start of data collection	Q3 2016
End of data collection	Q3 2016
Registration in the EU PAS register	Following ISAC protocol endorsement
Final report of study results:	Q4 2016

7. RATIONALE AND BACKGROUND

Type 2 diabetes mellitus (T2DM) is a global public health problem, affecting 415 million adults worldwide [R16-1233]. Currently it is estimated that about 3.9 million people in the United Kingdom (UK) have diabetes [R16-1232]. Glucose lowering drugs (GLDs), along with diet and exercise, can help to control T2DM-associated hyperglycaemia in adults and consequently delay development and slow progression of the microvascular complications of T2DM [R09-0481, P15-01174].

Jardiance (empagliflozin), a highly potent and selective inhibitor of the sodium-glucose cotransporter 2 (SGLT2), was approved in the EU for the treatment of T2DM in adults in May 2014 and Synjardy (empagliflozin/metformin HCl) in May 2015.

SGLT-2 is highly expressed in the kidney; as the predominant glucose transporter, it is responsible for the reabsorption of glucose from the glomerular filtrate back into the circulation. Empagliflozin improves glycaemic control in patients with T2DM by reducing renal glucose reabsorption [R14-4617]. Because of its recent market introduction, prescribing patterns associated with the use of empagliflozin in real-world settings remain unknown. Determining how GLDs are prescribed in clinical practice can provide valuable information on healthcare decision-making [R16-1230]. Furthermore, since the effectiveness and safety of empagliflozin and other non-insulin GLDs may be affected by demographic characteristics, medical comorbidities, and additional medications prescribed to T2DM patients, identifying the factors associated with the use of particular GLDs in real-world settings can provide important information needed for the future conduct of studies evaluating the comparative effectiveness and safety of glucose lowering drugs. In particular, such variables can be incorporated within propensity scores to help to minimize confounding by indication [P12-04844]. Furthermore, due to the mode of action, patients taking empagliflozin have experienced weight loss in clinical trials [P14-09057]. A theoretical possibility exists that empagliflozin may be used in patients without T2DM. Therefore, as part of the risk management plan (RMP), Boehringer Ingelheim (BI) has committed to conduct this drug utilization study (DUS) to assess the characteristics of patients initiating empagliflozin, including potential off-label use. Baseline characteristics of empagliflozin initiators will be compared to the characteristics of patients who started other non-insulin GLDs.

8. RESEARCH QUESTION AND OBJECTIVES

This study will be conducted within a cohort of patients initiating empagliflozin, other SGLT-2 inhibitors, and other commonly used non-insulin GLDs (metformin, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists) between 01 August 2014 through 01 September 2015 (Annex 3).

The objectives of this study are:

Primary: to describe and compare the general characteristics of patients with a recorded diagnosis of T2DM starting empagliflozin in the UK to the characteristics of patients with a recorded diagnosis of T2DM initiating other medications in the SGLT-2 inhibitor class and other non-insulin GLDs.

Secondary: to assess the extent of off-label use by identifying the proportion and describing the characteristics of patients initiating empagliflozin who do not have a recorded diagnosis for T2DM compared to patients without a recorded diagnosis for T2DM initiating other SGLT-2 inhibitors and other non-insulin GLDs.

9. RESEARCH METHODS

9.1 STUDY DESIGN

A cross-sectional study will be conducted in the UK Clinical Practice Research Datalink (CPRD). The study will use a "new users" or "incident users" design and will compare the baseline characteristics of new users of empagliflozin to the new users of other SGLT2 inhibitors or other commonly used non-insulin GLDs (metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 agonists).

The new-user design avoids comparing a population predominantly composed of first-time users of a newly marketed drug such as empagliflozin with a population of prevalent users of an older drug who may have stayed on the comparator treatment for a longer time [R14-2939]. Empagliflozin alone (Jardiance, ATC code A10BX12) or in fixed-dose combination (FDC) with metformin hydrochloride (Synjardy, ATC code A10BD20) will be the study drug of interest.

Patient characteristics will be tabulated for different exposure groups (empagliflozin, other SGLT-2 inhibitors, and other non-insulin GLDs) and different baseline statuses of diabetes codes (T2DM, T1DM, UDM, other types of diabetes, mixed diagnosis codes, gestational diabetes and breast feeding women, paediatrics, and patients without any diabetes diagnosis codes).

9.2 SETTING

9.2.1 Study population

Empagliflozin is expected to be prescribed mainly by general practitioners (GPs) and specialists, and most of the follow-up prescriptions (for chronic treatment) will also be issued by GPs or primary care physicians. Thus, the selected study populations will be individuals in the UK CPRD who have initiated empagliflozin, other SGLT-2 inhibitors, or other non-insulin GLDs (metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 agonists) during the study period.

9.2.2 Study period

The study period will start 01 August 2014 (the empagliflozin launch date in the UK) and end 01 September 2015.

9.2.3 Index prescription definition

The index prescription will be the first prescription for empagliflozin, other SGLT2 inhibitors, or non-insulin GLDs (metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 agonists) during the study period (01 August 2014 – 01 September 2015). Index prescriptions of the study drugs include the single study drugs or fixed-dose combinations (FDC) of the study drugs with metformin when available (Annex 3).

9.2.4 Index date

The index date will be defined as the date on which each identified new user receives the index prescription.

9.2.5 Baseline and look-back period

To characterize the empagliflozin, other SGLT2 inhibitor, or non-insulin GLD initiators, all information available during the look-back (pre-index) time period will be collected. The look-back time period is defined as the time period ending on the day before the index date. Since all study participants are required by inclusion criteria to have at least 12 months of data before the index date (baseline period), the look-back time period will include at least 365 days during which covariates can be evaluated. For some of the study population, more data on covariates might be available beyond 365 days, and all available information will be considered for covariate classification related to diabetes, diabetes medications, and concomitant chronic conditions. Nevertheless, for concomitant medications used for diseases other than diabetes, the look-back time period will be limited to 180 days prior to the index date to increase the likelihood that the medications were used concomitantly.

If the distribution of the duration of look-back time is different among empagliflozin, other SGLT2 inhibitor, and non-insulin GLDs initiators, categories of look-back time will be created using indicator variables. Those indicator variables will then be used as covariates in the multivariable regression models for propensity score development, to control for possible differences in availability of information between the empagliflozin and comparator cohorts.

9.2.6 Inclusion and exclusion criteria

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

At least 12 months of continuous registration prior to the index date in a practice contributing up to standard (UTS) data to the CPRD. Infants younger than 1 year will not be required to have 12 months of continuous UPS registration in the CPRD.

A new user of one of the index prescriptions (empagliflozin, other SGLT2 inhibitor, or non-insulin GLDs) or a FDC with metformin.

There is no exclusion criterion in this study.

9.3 VARIABLES

9.3.1 Exposures

Empagliflozin alone (Jardiance, ATC code A10BX12) or in fixed-dose combination (FDC) with metformin hydrochloride (Synjardy, ATC code A10BD20) will be the study drug of interest. Other SGLT2 inhibitors or other commonly used non-insulin GLDs (metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 agonists) are comparators in this study (Annex 3).

To avoid the inclusion of prevalent users:

SGLT2 inhibitor initiators will be required to have no exposure to SGLT2 inhibitors during the 12 months pre-index period.

DPP-4 inhibitors initiators will be required to have no exposure to DPP-4 inhibitors during the 12 months pre-index period.
Metformin initiators will be required to have no exposure to metformin during the 12 months pre-index period.
Sulfonylureas initiators will be required to have no exposure to sulfonylureas during the 12 months pre-index period.
GLP-1 agonists initiators will be required to have no exposure to GLP-1 agonists during the 12 months pre-index period.

Patients initiating more than 1 index prescription (a combination) at the index date will enter the cohorts of each of the respective drugs independently.

9.3.2 Outcomes

This is a study to describe the general characteristics of patients with (or without) a recorded diagnosis of T2DM starting empagliflozin (other SGLT-2 inhibitors or non-insulin GLDs) in the UK between August 2014 and September 2015.
For all included patients, the whole look-back period will be checked to identify all recorded diagnosis codes in Annex 4. Patients will be categorized based on the available diagnosis codes in CPRD (see Table 1) and their baseline characteristics will be measured and compared between different exposure categories:

Table 1 Classification of baseline diabetes status based on the available codes in CPRD

Baseline diabetes status		Diagnosis codes
T2DM	Probable	Patients with 2 or more T2DM Read Codes on different dates (patients with the following read codes will be excluded from this category: T1DM, MODY, LADA, GD, secondary diabetes, other diabetes, and pregnant and breast feeding women)
	Possible	Patients with only one T2DM Read Code + one or more "unspecified" DM Read Codes on different dates (patients with the following read codes will be excluded from this category: T1DM, MODY, LADA, GD, secondary diabetes, other diabetes, and pregnant and breast feeding women)
	Likely	Patients with only one T2DM Read Code
T1DM	Probable	Patients with 2 or more T1DM Read Codes on different dates (patients with the following read codes will be excluded from this category: T2DM, MODY, LADA, GD, secondary diabetes, other diabetes, and pregnant and breast feeding women)
	Possible	Patients with only one T1DM Read Code + 1 or more "unspecified" DM Read Codes on different dates (patients with the following read codes will be excluded from this category: T2DM, MODY, LADA, GD, secondary diabetes, other diabetes, and pregnant and breast feeding women)
	Likely	Patients with only one T1DM Read Code
Unspecified		Patients who only had "unspecified" DM Read Codes in tables Clinical and/or Referral (patients with the following read codes will be excluded from this category: T2DM, T1DM, MODY, LADA, GD, secondary diabetes, other diabetes, and pregnant and breast feeding women)

Table 1 (cont'd) Classification of baseline diabetes status based on the available codes in CPRD

Baseline diabetes status		Diagnosis codes
Other types of diabetes	Maturity onset Diabetes of the young (MODY)	Patients with MODY Read Code ± "unspecified" DM Read Codes (patients with the following read codes will be excluded from this category: T2DM, T1DM, LADA, GD, secondary diabetes, other diabetes, and pregnant and breast feeding women)
	Latent autoimmune diabetes of adults (LADA)	Patients with LADA Read Code ± "unspecified" DM Read Codes (patients with the following read codes will be excluded from this category: T2DM, T1DM, MODY,GD, secondary diabetes, other diabetes, and pregnant and breast feeding women)
	Secondary	Patients who only had secondary diabetes Read Codes (patients with the following read codes will be excluded from this category: T2DM, T1DM, MODY, LADA, GD, other diabetes, and pregnant and breast feeding women)
	Other DM types	Patients with OTHER Read Code ± "unspecified" DM Read Codes (patients with the following read codes will be excluded from this category: T2DM, T1DM, LADA, MODY, GD, secondary diabetes and pregnant and breast feeding women)
Mixed DM		Patients who had a combination of different diabetes codes (T1DM or T2DM or MODY or LADA, GD etc.)
Gestational diabetes (GD), pregnant or breast feeding women		Patients with GD Read Codes or women who were pregnant or registered as breast feeding at the index date
Without any diabetes diagnosis codes		Patients without any diagnosis codes mentioned above

Depending on the number of patients, "possible" and "likely" categories might be merged.

9.3.3 Covariates

The following baseline characteristics will be identified:
Demographics
Life style factors
Laboratory tests
Comorbidities
Concomitant medications

All details can be found in Annex 5.
All available information will be considered for covariate classification related to diabetes, diabetes complications and medications, and concomitant chronic conditions. For concomitant medications used for diseases other than diabetes the look-back time period will be limited to 180 days prior to the index date to increase the likelihood that the medications were used concomitantly. Concomitant medications (diabetes or non-diabetes medications) will be categorized as current use (up to and including 60 days before index date) and past use (use any time prior to the 60 days before index date).

9.4 DATA SOURCES

In the UK, nearly all residents are registered in a general medical practice that uses electronic medical records. Some of those records are available for research purposes in the CPRD. CPRD contains diagnostic and prescribing information recorded by general practitioners (GPs) as part of their routine clinical practice in the UK. The database currently contains data for over 13.2 million patients with research-quality data from 680 UK practices; 5.69 million of these patients are active (still registered with a contributing GP practice) [R14-5257]. Patients registered are representative of the whole UK population in terms of age and sex. A large proportion of patients are linkable to central mortality records.

Detailed information on prescriptions written by GPs, including prescribed dose and duration, is routinely recorded in the data source. Read codes are used for diagnoses, and Gemscript codes are used for medications.

The CPRD contains information on lifestyle factors with a variable proportion of missing values. For example, data on body weight and height, smoking, and alcohol use were available for approximately 70% of patients in the CPRD [R14-5279]. In contrast, the pharmaceutical exposures and comorbidities are expected to be based on outpatient prescriptions and to be complete.

9.5 STUDY SIZE

The study size will be driven by the uptake of empagliflozin following approval and launch of empagliflozin for the treatment of T2DM to improve glycaemic control in adults in the UK. A feasibility assessment, performed using CPRD data through 01 September 2015, identified 169 patients treated with empagliflozin.

The precision of proportion estimates (e.g. prevalence, see table 2) is a function of the proportion and the number of patients contributing to the proportion (standard error = square

root[p(1-p)/n]). Therefore the precision for a prevalence estimate of 10% or 20% is less 5% even for the sample size that will likely be present in this study.

Table 2 Precision of estimates for proportion measures

Numerator	Denominator	Prevalence	95% CI	Standard error
10	100	10%	4.1%-15.9%	3.0%
100	1,000	10%	8.2%-11.8%	0.9%
1,000	10,000	10%	9.4%-10.6%	0.3%
20	100	20%	12.1%-27.8%	4.0%
200	1,000	20%	17.5%-22.6%	1.3%
2,000	10,000	20%	19.2%-20.8%	0.4%

95% CI = P+/- 1.96 SE

For continuous measures, the precision depends on the number of subjects on whom the estimate is made and the variability of the measures (standard error = square root[standard deviation^2/n]). Therefore the precision is sufficiently high for all continuous parameters (see table 3).

Table 3 Precision of estimates for continuous measures

Sample size	Mean	SD	Standard error
100	1	0.5	5.0%
1,000	1	0.5	1.6%
10,000	1	0.5	0.5%

9.6 DATA MANAGEMENT

Full audit trail starting from raw data, and ending with statistical tables and graphs in reports will be maintained. Data management, tabulations, graphics, and statistical modelling will be carried out with latest updated version of Aetion Evidence Platform. Source code of data management and data analyses will be kept for inspection at least for five years after publication of the results. A program specification document (PSD) detailing all statistical analyses and measure definitions in Aetion Evidence Platform will be developed and used as a basis for analysis.

All study related datasets will be stored in a secured server environment. Access to data will be permitted only to study statisticians and data managers in line with the data permits. All data used for this study will be anonymous such that no study individual can be directly identified. Data will be regularly backed-up and stored in a separate secure location.

9.7 DATA ANALYSIS

The analysis will be largely descriptive and include baseline data only. Final approach to data analysis will be presented in a separate program specification document (PSD) to be developed prior to the start of data analysis.

9.7.1 Main analysis

The primary analysis will focus on the baseline characteristics (demographic, medical and prescription history) of the exposure category of interest (empagliflozin). These characteristics will be compared to the characteristics of patients in other exposure categories (other SGLT2 inhibitors and commonly used non-insulin GLDs (metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 agonists). Patients in different exposure categories will be stratified according to their baseline diabetes status based upon diabetes Read codes (T2DM, T1DM, UDM, other types of diabetes, mixed diagnosis codes, gestational diabetes and breast feeding women, paediatrics, and patients without any diabetes diagnosis codes). All the above categories will be stratified into paediatrics (<18 years of age) and adults (≥18 years of age).

Following recommendation of CPRD Independent Scientific Advisory Committee (ISAC), when reporting the data, CPRD policy is that no cell should contain <5 events.

Results will be presented as means, standard deviations, medians, minimum, maximum, and interquartile range (IQR) for continuous variables, and as counts and percentages for categorical variables. Analyses will be conducted in unmatched cohorts and differences between empagliflozin and each of the other exposure groups will be assessed using absolute standardized differences (ASD), where an ASD of at least 10% will be considered a meaningful difference [R13-3590, R16-1228, R16-1227, R16-1709].

Empagliflozin is usually a second- or third-line treatment for T2DM; and for the majority of patients, empagliflozin will be added to an existing treatment. Therefore, additional analysis will be done to classify patients according to their treatment complexity as receiving mono vs. dual vs. triple combination therapy and naïve versus non-naïve treatment status. Patients with no use of any glucose lowering medicine (including insulin) in the prior 6 months will be defined as treatment naïve patients.

The prevalence (with 95% CI) of potential off-label use (patients without any recorded T2DM Read Code) among new users of empagliflozin, other SGLT2 inhibitor, and other non-insulin GLD initiators during the overall study period will be calculated by dividing the number of potential off-label users by the total population in that exposure category. The proportion of identified users in the paediatric age subgroup will be described.

9.7.2 Missing values

In the CPRD, no high frequency of missing values is expected for most variables, with the possible exception of lifestyle variables. For all covariates, missing values will be presented as a separate category.

9.8 QUALITY CONTROL

The study will be conducted as specified in this protocol and a separate program specification document (PSD). All revisions to the protocol shall be properly documented as protocol changes.

The study protocol has been written following the Code of Conduct by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) [R15-4870] that provides a set of rules and principles for post-authorisation studies with regard to the best practices and transparency, thereby promoting scientific independence of such studies. The study will be registered to the ENCePP's E-register and the results will also be published on the same site.

The study protocol also follows the key elements of the Guideline for Good Pharmacoepidemiology Practices by International Society for Pharmacoepidemiology [R11-4318], and the recent draft Guidance for Industry and FDA Staff "Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets" [R15-4859].

The program specification document (PSD) including details of cohort definitions, patient selector, and analysis parameters will be written and finalized before the start of analysis. The Aetion analytic approach will be reviewed/repeated by a second analyst to ensure quality control.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Pharmacy dispensing data is generally considered to be of higher accuracy than self-report or physician notes [P13-03078, P13-03077], therefore there is limited potential for misclassification and measurement bias with regard to drug exposures. All patients with T2DM may not be captured. Patients were categorized based on the available diagnosis codes for different types of diabetes, therefore misclassification and measurement bias of types of diabetes is possible. However, patients were categorized cautiously based on all available diagnosis codes to reduce the probability of misclassification.
In addition misclassification of comorbidities can be expected, however this misclassification will be minimized by using all available data pre-index date [R14-1409].

Some potentially important variables, including smoking status, BMI, alcohol use, blood pressure, lab tests, exercise, and non-prescription drug use, may not be recorded or may not be properly recorded within the database. Missing values will be recorded as a separate category.

10. PROTECTION OF HUMAN SUBJECTS

This is a non-interventional study using an existing database (secondary data) and does not pose any risks for patients. All data collected in the study will be de-identified with no breach of confidentiality with regard to personal identifiers or health information. Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

BI will submit the final study protocol for approval to the Independent Scientific Advisory Committee (ISAC) (http://www.cprd.com/ISAC). The CPRD has obtained ethical approval from a Multicentre Research Ethics Committee for all observational research using CPRD data without patient involvement; however, ISAC may recommend that the Multicentre Research Ethics Committee review the study documentation if any ethical issues arise.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Based on current guidelines from the International Society for Pharmacoepidemiology [R11-4318] and the EMA [R13-1970], non-interventional studies such as the one described in this protocol, conducted using medical chart reviews or electronic claims and health care records, do not require expedited reporting of suspected adverse events/reactions. Specifically, as stated in section VI.C.1.2.1 of Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Management and Reporting of Adverse Reactions to Medicinal Products, for non-interventional study designs, which are based on use of secondary data, reporting of adverse reactions is not required.

The data generated in the course of the study will be monitored by the BI responsible person.

When an observation is identified that may qualify as a special safety issue or that may have implications for the benefit-risk balance of empagliflozin, appropriate BI functions will be notified according to BI standard operating procedures (SOPs).

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study report will be prepared using a template following the Guideline on Good Pharmacovigilance Practices (GVP), Module VIII, Section B.6.3 [R13-5420]. The final report will be will be submitted to the EMA and reported within the earliest corresponding Periodic Safety Update Report and Risk Management Plan update.

Scientific manuscript(s) describing this work will be submitted for publication in peer-reviewed journals. Any publications will follow guidelines, including those for authorship, established by the International Committee of Medical Journal Editors [R13-5418]. When reporting results of this study, the appropriate STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist will be followed [R13-2485].Findings may also be submitted for presentation at scientific conferences.

13. REFERENCES

13.1 PUBLISHED REFERENCES

R15-4870	ENCePP. The ENCePP Code of Conduct for Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance Studies. 21 November 2011, EMA/929209/2011. www.encepp.eu/code_of_conduct/documents/CodeofConduct_Rev2.pdf
R16-1231	Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, Staa T van, Smeeth L. Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol 2015*; 44 (3): 827 – 836.
R13-3590	Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat 2011*; 10 (2): 150 – 161.
R16-1228	Ali MS, Groenwold RHH, Pestman WR, Belitser SV, Roes KC, Hoes AW, Boer A de, Klungel OH. Propensity score balance measures in pharmacoepidemiology: a simulation study. *Pharmacoepidemiol Drug Saf 2014*; 23 (8): 802 – 811.
R16-1227	Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med 2009*; 28 (25): 3083 – 3107.
R16-1709	Mamdani M, Sykora K, Li P, Normand SLT, Streiner DL, Austin PC, Rochon PA, Anderson GM. Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. Br Med J 2005; 330 (7497): 960 – 962.
R16-1233	Executive summary. In: International Diabetes Federation. IDF diabetes atlas. 7th ed. Brussels: International Diabetes Federation 2015. http://www.diabetesatlas.org (access date: 21 March 2016).
R16-1232	Diabetes: facts and stats, version 4 (revised: May 2015). https://www.mrc.ac.uk/documents/pdf/diabetes-uk-facts-and-stats-june-2015/ (access date: 21 March 2016).
R09-0481	Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, Wiley C, Selvin E, Wilson R, Bass EB, Brancati FL. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med 2007*; 147: 386 - 399.
P15-01174	Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care 2015*; 38 (1): 140 – 149.

R14-4617	Boehringer Ingelheim International GmbH. Jardiance (empagliflozin) summary of product characteristics. 2014. Available at: website: ema.europa.eu/ema/index.jsp?curl = pages/medicines/human/medicines/002677/human_med_001764.jsp&mid = WC0b01ac058001d124. Accessed 09 October 2014.
R16-1230	Khan GH, Aqil M, Pillai KK, Ahmad A, Kapur P, Ain R, Al-Ghamdi SS, Shahzad N. Therapeutic adherence: a prospective drug utilization study of oral hypoglycemic in patients with type 2 diabetes mellitus. *Asian Pac J Trop Dis 2014*; 4 (Suppl 1): S347 - S352.
P12-04844	Glynn RJ, Schneeweiss S, Sturmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol 2006*; 98: 253 – 259.
P14-09057	Rosenstock J, Jelaska A, Frappin G, Salsali A, Kim G, Woerle HJ, Broedl UC, EMPA-REG MDI Trial Investigators. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. *Diabetes Care 2014*; 37: 1815 – 1823.
R14-2939	Johnson ES, Bartman BA, Briesacher BA, Fleming NS, Gerhard T, Kornegay CJ, Nourjah P, Sauer B, Schumock GT, Sedrakyan A, Sturmer T, West SL, Schneeweiss S. The incident user design in comparative effectiveness research. *Pharmacoepidemiol Drug Saf 2013*; 22 (1): 1 – 6.
R14-5257	ISAC. Annual report Jan 2013-Dec 2013. Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency (MHRA) for database research; 2013. Available at: website: mhra.gov.uk/home/groups/pla/documents/committeedocument/con448379.pdf. Accessed 14 October 2014.
R14-5279	Gelfand JM, Margolis DJ, Dattani H. The UK General Practice Research Database. In: Strom BL, editor. Pharmacoepidemiology, 4th ed: *John Wiley & Sons; 2005*. p. 337-46.
R11-4318	ISPE, International Society for Pharmacoepidemiology. Guidelines for Good Pharmacoepidemiological Practices. Revision 2: April 2007. www.pharmacoepi.org/resources/guidelines_08027.cfm.
R15-4859	FDA, Food and Drug Administration. Guidance for Industry and FDA Staff. Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets. February 2011. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf
P13-03078	West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A. Recall accuracy for prescription medications: self-report compared with database information. *Am J Epidemiol 1995*; 142 (10): 1103 – 1112.
P13-03077	West SL, Strom BL, Freundlich B, Normand E, Koch G, Savitz DA.

	Completeness of prescription recording in outpatient medical records from a health maintenance organization. *J Clin Epidemiol 1994*; 47 (2): 165 – 171.
R14-1409	Brunelli SM, Gagne JJ, Huybrechts KF, Wang SV, Patrick AR, Rothman KJ, Seeger JD. Estimation using all available covariate information versus a fixed look-back window for dichotomous covariates. *Pharmacoepidemiol Drug Saf 2013*; 22: 542 – 550.
R13-1970	EMA. Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products. European Medicines Agency; 22 June 2012. Available at: website: emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129135.pdf. Accessed 7 February 2013.
R13-5420	EMA. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies. European Medicines Agency; 9 July 2012. Available at: website: emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf. Accessed 7 February 2013.
R13-5418	ICMJE. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. International Committee of Medical Journal Editors; August 2013. Available at: website: icmje.org/urm_main.html. Accessed 25 February 2014.
R13-2485	Elm E von, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, STROBE Initiative. The Strengthening the rRporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007; 370: 1453 – 1457.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

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

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

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

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

Study title:
Characteristics of patients initiating empagliflozin or other non-insulin glucose lowering drugs in the United Kingdom

Study reference number:
Study not registered yet.

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

Comments:

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

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☐	☐	☒	-
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7.1

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

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	-
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	9.2
	4.2.2 Age and sex?	☒	☐	☐	9.2
	4.2.3 Country of origin?	☒	☐	☐	9.2
	4.2.4 Disease/indication?	☒	☐	☐	9.3
	4.2.5 Duration of follow-up?	☐	☐	☒	-
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	-
5.3	Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	-
5.4	Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	-

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	-
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	-

Comments:

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

Comments:

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

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.2
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.2
9.1.3 Covariates?	☒	☐	☐	9.2
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.2
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.2
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.2
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Annex 3
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Annex 4
9.3.3 Covariates?	☒	☐	☐	Annex 5
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	-

Comments:

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

Comments:

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

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5

Comments:

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

Comments:

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

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

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

Date: 04/August/2016

Signature: [redacted]

ANNEX 3. CODES TO IDENTIFY EXPOSURE VARIABLES

No.	Exposure category	Variable	ATC codes
1	Empagliflozin (Exposure of interest)	Empagliflozin	A10BX12
		FDCM**	A10BD20
2	Other SGLT2 inhibitors	Canagliflozin	A10BX11
		Dapagliflozin	A10BX09
		Canagliflozin FDCM**	A10BD16
		Dapagliflozin FDCM**	A10BD15
3	DPP-4 inhibitors	Alogliptin	A10BH04
		Linagliptin	A10BH05
		Saxagliptin	A10BH03
		Sitagliptin	A10BH01
		Vildagliptin	A10BH02
		Alogliptin FDCM**	A10BD13
		Linagliptin FDCM**	A10BD11
		Saxagliptin FDCM**	A10BD10
		Sitagliptin FDCM**	A10BD12
		Vildagliptin FDCM**	A10BD08
4	Metformin	Metformin	A10BA02
5	Sulphonylureas	Sulphonylureas	ATC beginning with A10BB (including Glymidine sodium with ATC code of A10BC01)
6	Glucagon-like peptide-1 agonists	Exenatide	A10BX04
		Liraglutide	A10BX07
		Lixisenatide	A10BX10
		Dulaglutide	A10BX14

FDCM** — Fixed dose combination with metformin

ANNEX 4. READ CODES TO IDENTIFY THE BASELINE DIABETES STATUS OF STUDY PARTICIPANTS

Medcode	Read code	Description
Type 2 diabetes mellitus (T2DM)		
83532	66Ao.00	Diabetes type 2 review
101801	66At100	Type II diabetic dietary review
102611	66At111	Type 2 diabetic dietary review
93657	8Hj4.00	Referral to DESMOND diabetes structured education programme
95093	8I83.00	Did not complete DESMOND diabetes structured educat program
95159	9NiD.00	Did not attend DESMOND diabetes structured education program
93529	9OLK.00	DESMOND diabetes structured education programme completed
506	C100112	Non-insulin dependent diabetes mellitus
56803	C107400	NIDDM with peripheral circulatory disorder
5884	C109.11	NIDDM - Non-insulin dependent diabetes mellitus
17859	C109.12	Type 2 diabetes mellitus
18219	C109.13	Type II diabetes mellitus
52303	C109000	Non-insulin-dependent diabetes mellitus with renal comps
50225	C109011	Type II diabetes mellitus with renal complications
18209	C109012	Type 2 diabetes mellitus with renal complications
50429	C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
59725	C109111	Type II diabetes mellitus with ophthalmic complications
70316	C109112	Type 2 diabetes mellitus with ophthalmic complications
55842	C109200	Non-insulin-dependent diabetes mellitus with neuro comps
67905	C109211	Type II diabetes mellitus with neurological complications
45919	C109212	Type 2 diabetes mellitus with neurological complications
62146	C109300	Non-insulin-dependent diabetes mellitus with multiple comps
108005	C109312	Type 2 diabetes mellitus with multiple complications
34912	C109400	Non-insulin dependent diabetes mellitus with ulcer

Medcode	Read code	Description
55075	C109411	Type II diabetes mellitus with ulcer
65704	C109412	Type 2 diabetes mellitus with ulcer
40401	C109500	Non-insulin dependent diabetes mellitus with gangrene
62107	C109511	Type II diabetes mellitus with gangrene
46150	C109512	Type 2 diabetes mellitus with gangrene
17262	C109600	Non-insulin-dependent diabetes mellitus with retinopathy
58604	C109611	Type II diabetes mellitus with retinopathy
42762	C109612	Type 2 diabetes mellitus with retinopathy
8403	C109700	Non-insulin dependent diabetes mellitus - poor control
24458	C109711	Type II diabetes mellitus - poor control
45913	C109712	Type 2 diabetes mellitus - poor control
29979	C109900	Non-insulin-dependent diabetes mellitus without complication
105784	C109912	Type 2 diabetes mellitus without complication
72320	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
50813	C109A11	Type II diabetes mellitus with mononeuropathy
45467	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
47409	C109B11	Type II diabetes mellitus with polyneuropathy
59365	C109C00	Non-insulin dependent diabetes mellitus with nephropathy
64571	C109C11	Type II diabetes mellitus with nephropathy
24836	C109C12	Type 2 diabetes mellitus with nephropathy
43785	C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
56268	C109D11	Type II diabetes mellitus with hypoglycaemic coma
61071	C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
69278	C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
48192	C109E11	Type II diabetes mellitus with diabetic cataract
44779	C109E12	Type 2 diabetes mellitus with diabetic cataract
54212	C109F00	Non-insulin-dependent d m with peripheral angiopath
54899	C109F11	Type II diabetes mellitus with peripheral angiopathy
60699	C109F12	Type 2 diabetes mellitus with peripheral angiopathy
24693	C109G00	Non-insulin dependent diabetes mellitus with arthropathy
18143	C109G11	Type II diabetes mellitus with arthropathy

Medcode	Read code	Description
49869	C109G12	Type 2 diabetes mellitus with arthropathy
40962	C109H00	Non-insulin dependent d m with neuropathic arthropathy
47816	C109H11	Type II diabetes mellitus with neuropathic arthropathy
66965	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
18278	C109J00	Insulin treated Type 2 diabetes mellitus
37648	C109J11	Insulin treated non-insulin dependent diabetes mellitus
18264	C109J12	Insulin treated Type II diabetes mellitus
36633	C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
758	C10F.00	Type 2 diabetes mellitus
22884	C10F.11	Type II diabetes mellitus
18777	C10F000	Type 2 diabetes mellitus with renal complications
57278	C10F011	Type II diabetes mellitus with renal complications
47321	C10F100	Type 2 diabetes mellitus with ophthalmic complications
100964	C10F111	Type II diabetes mellitus with ophthalmic complications
34268	C10F200	Type 2 diabetes mellitus with neurological complications
98616	C10F211	Type II diabetes mellitus with neurological complications
65267	C10F300	Type 2 diabetes mellitus with multiple complications
43227	C10F311	Type II diabetes mellitus with multiple complications
49074	C10F400	Type 2 diabetes mellitus with ulcer
91646	C10F411	Type II diabetes mellitus with ulcer
12736	C10F500	Type 2 diabetes mellitus with gangrene
104323	C10F511	Type II diabetes mellitus with gangrene
18496	C10F600	Type 2 diabetes mellitus with retinopathy
49655	C10F611	Type II diabetes mellitus with retinopathy
25627	C10F700	Type 2 diabetes mellitus - poor control
47315	C10F711	Type II diabetes mellitus - poor control
47954	C10F900	Type 2 diabetes mellitus without complication
53392	C10F911	Type II diabetes mellitus without complication
62674	C10FA00	Type 2 diabetes mellitus with mononeuropathy
95351	C10FA11	Type II diabetes mellitus with mononeuropathy
18425	C10FB00	Type 2 diabetes mellitus with polyneuropathy

Medcode	Read code	Description
50527	C10FB11	Type II diabetes mellitus with polyneuropathy
12640	C10FC00	Type 2 diabetes mellitus with nephropathy
102201	C10FC11	Type II diabetes mellitus with nephropathy
46917	C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
98723	C10FD11	Type II diabetes mellitus with hypoglycaemic coma
44982	C10FE00	Type 2 diabetes mellitus with diabetic cataract
93727	C10FE11	Type II diabetes mellitus with diabetic cataract
37806	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
104639	C10FF11	Type II diabetes mellitus with peripheral angiopathy
59253	C10FG00	Type 2 diabetes mellitus with arthropathy
103902	C10FG11	Type II diabetes mellitus with arthropathy
35385	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
1407	C10FJ00	Insulin treated Type 2 diabetes mellitus
64668	C10FJ11	Insulin treated Type II diabetes mellitus
34450	C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
107701	C10FK11	Hyperosmolar non-ketotic state in type II diabetes mellitus
26054	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
60796	C10FL11	Type II diabetes mellitus with persistent proteinuria
18390	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
85991	C10FM11	Type II diabetes mellitus with persistent microalbuminuria
32627	C10FN00	Type 2 diabetes mellitus with ketoacidosis
106528	C10FN11	Type II diabetes mellitus with ketoacidosis
51756	C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
106061	C10FP11	Type II diabetes mellitus with ketoacidotic coma
25591	C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
63690	C10FR00	Type 2 diabetes mellitus with gastroparesis
107824	C10P100	Type II diabetes mellitus in remission
50609	L180600	Pre-existing diabetes mellitus, non-insulin-dependent
25041	ZC2CA00	Dietary advice for type II diabetes
4513	C109.00	Non-insulin dependent diabetes mellitus
109103	C109911	Type II diabetes mellitus without complication

Medcode	Read code	Description
109865	C109B12	Type 2 diabetes mellitus with polyneuropathy
109197	C10FH11	Type II diabetes mellitus with neuropathic arthropathy
Type 1 diabetes mellitus (T1DM)		
85660	66An.00	Diabetes type 1 review
102704	66At000	Type I diabetic dietary review
104453	66At011	Type 1 diabetic dietary review
93704	8Hj3.00	Referral to DAFNE diabetes structured education programme
97809	8I82.00	Did not complete DAFNE diabetes structured education program
106953	8IEa.00	Referral to DAFNE diabetes structured educn prog declined
99277	9NiC.00	Did not attend DAFNE diabetes structured education programme
93390	9OLH.00	Attended DAFNE diabetes structured education programme
93491	9OLJ.00	DAFNE diabetes structured education programme completed
24490	C100000	Diabetes mellitus, juvenile type, no mention of complication
1038	C100011	Insulin dependent diabetes mellitus
53200	C101000	Diabetes mellitus, juvenile type, with ketoacidosis
40023	C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
42567	C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
93922	C104000	Diabetes mellitus, juvenile type, with renal manifestation
69748	C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
67853	C106000	Diabetes mellitus, juvenile, + neurological manifestation
70448	C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
69124	C107300	IDDM with peripheral circulatory disorder
1647	C108.00	Insulin dependent diabetes mellitus
18505	C108.11	IDDM-Insulin dependent diabetes mellitus
17858	C108.12	Type 1 diabetes mellitus
24423	C108.13	Type I diabetes mellitus
46963	C108000	Insulin-dependent diabetes mellitus with renal complications
61344	C108011	Type I diabetes mellitus with renal complications
21983	C108012	Type 1 diabetes mellitus with renal complications
49276	C108100	Insulin-dependent diabetes mellitus with ophthalmic comps

Medcode	Read code	Description
102740	C108112	Type 1 diabetes mellitus with ophthalmic complications
52283	C108200	Insulin-dependent diabetes mellitus with neurological comps
49146	C108211	Type I diabetes mellitus with neurological complications
61829	C108212	Type 1 diabetes mellitus with neurological complications
52104	C108300	Insulin dependent diabetes mellitus with multiple complicatn
108007	C108311	Type I diabetes mellitus with multiple complications
26855	C108400	Unstable insulin dependent diabetes mellitus
60107	C108411	Unstable type I diabetes mellitus
97474	C108412	Unstable type 1 diabetes mellitus
44443	C108500	Insulin dependent diabetes mellitus with ulcer
51957	C108511	Type I diabetes mellitus with ulcer
68390	C108512	Type 1 diabetes mellitus with ulcer
60499	C108600	Insulin dependent diabetes mellitus with gangrene
6509	C108700	Insulin dependent diabetes mellitus with retinopathy
38161	C108711	Type I diabetes mellitus with retinopathy
41049	C108712	Type 1 diabetes mellitus with retinopathy
6791	C108800	Insulin dependent diabetes mellitus - poor control
46850	C108811	Type I diabetes mellitus - poor control
45914	C108812	Type 1 diabetes mellitus - poor control
56448	C108A00	Insulin-dependent diabetes without complication
95992	C108A11	Type I diabetes mellitus without complication
24694	C108B00	Insulin dependent diabetes mellitus with mononeuropathy
99231	C108B11	Type I diabetes mellitus with mononeuropathy
41716	C108C00	Insulin dependent diabetes mellitus with polyneuropathy
57621	C108D00	Insulin dependent diabetes mellitus with nephropathy
66872	C108D11	Type I diabetes mellitus with nephropathy
44440	C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
42729	C108E11	Type I diabetes mellitus with hypoglycaemic coma
70766	C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
44260	C108F00	Insulin dependent diabetes mellitus with diabetic cataract
17545	C108F11	Type I diabetes mellitus with diabetic cataract

Medcode	Read code	Description
64446	C108G00	Insulin dependent diab mell with peripheral angiopathy
65616	C108H00	Insulin dependent diabetes mellitus with arthropathy
62352	C108H11	Type I diabetes mellitus with arthropathy
39809	C108J00	Insulin dependent diab mell with neuropathic arthropathy
60208	C108J11	Type I diabetes mellitus with neuropathic arthropathy
18230	C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
1549	C10E.00	Type 1 diabetes mellitus
12455	C10E.11	Type I diabetes mellitus
51261	C10E.12	Insulin dependent diabetes mellitus
47582	C10E000	Type 1 diabetes mellitus with renal complications
102946	C10E012	Insulin-dependent diabetes mellitus with renal complications
47649	C10E100	Type 1 diabetes mellitus with ophthalmic complications
99311	C10E111	Type I diabetes mellitus with ophthalmic complications
98071	C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
42831	C10E200	Type 1 diabetes mellitus with neurological complications
101735	C10E212	Insulin-dependent diabetes mellitus with neurological comps
47650	C10E300	Type 1 diabetes mellitus with multiple complications
91942	C10E311	Type I diabetes mellitus with multiple complications
45276	C10E312	Insulin dependent diabetes mellitus with multiple complicat
43921	C10E400	Unstable type 1 diabetes mellitus
49949	C10E411	Unstable type I diabetes mellitus
54600	C10E412	Unstable insulin dependent diabetes mellitus
18683	C10E500	Type 1 diabetes mellitus with ulcer
93878	C10E511	Type I diabetes mellitus with ulcer
98704	C10E512	Insulin dependent diabetes mellitus with ulcer
69993	C10E600	Type 1 diabetes mellitus with gangrene
102112	C10E611	Type I diabetes mellitus with gangrene
18387	C10E700	Type 1 diabetes mellitus with retinopathy
95343	C10E711	Type I diabetes mellitus with retinopathy
93875	C10E712	Insulin dependent diabetes mellitus with retinopathy
35288	C10E800	Type 1 diabetes mellitus - poor control

Medcode	Read code	Description
105337	C10E811	Type I diabetes mellitus - poor control
72702	C10E812	Insulin dependent diabetes mellitus - poor control
69676	C10EA00	Type 1 diabetes mellitus without complication
62613	C10EA11	Type I diabetes mellitus without complication
99719	C10EA12	Insulin-dependent diabetes without complication
68105	C10EB00	Type 1 diabetes mellitus with mononeuropathy
46301	C10EC00	Type 1 diabetes mellitus with polyneuropathy
91943	C10EC11	Type I diabetes mellitus with polyneuropathy
101311	C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
10418	C10ED00	Type 1 diabetes mellitus with nephropathy
102163	C10ED12	Insulin dependent diabetes mellitus with nephropathy
39070	C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
99716	C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma
49554	C10EF00	Type 1 diabetes mellitus with diabetic cataract
100770	C10EF12	Insulin dependent diabetes mellitus with diabetic cataract
93468	C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
18642	C10EH00	Type 1 diabetes mellitus with arthropathy
54008	C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
30323	C10EK00	Type 1 diabetes mellitus with persistent proteinuria
30294	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
102620	C10EL11	Type I diabetes mellitus with persistent microalbuminuria
10692	C10EM00	Type 1 diabetes mellitus with ketoacidosis
62209	C10EM11	Type I diabetes mellitus with ketoacidosis
40837	C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
66145	C10EN11	Type I diabetes mellitus with ketoacidotic coma
22871	C10EP00	Type 1 diabetes mellitus with exudative maculopathy
97894	C10EP11	Type I diabetes mellitus with exudative maculopathy
55239	C10EQ00	Type 1 diabetes mellitus with gastroparesis
108360	C10P000	Type I diabetes mellitus in remission
68792	C10z000	Diabetes mellitus, juvenile type, + unspecified complication
50960	L180500	Pre-existing diabetes mellitus, insulin-dependent

Medcode	Read code	Description
69043	ZC2C900	Dietary advice for type I diabetes
32359	ZRbH.00	Perceived control of insulin-dependent diabetes
110400	C108F12	Type 1 diabetes mellitus with diabetic cataract
109837	C10E011	Type I diabetes mellitus with renal complications
109051	C10E612	Insulin dependent diabetes mellitus with gangrene
108724	C10EQ11	Type I diabetes mellitus with gastroparesis
109628	C10P011	Type 1 diabetes mellitus in remission
109878	ZC2C911	Diet advice for insulin-dependent diabetes
Unspecified diabetes mellitus (UDM)		
21689	13AB.00	Diabetic lipid lowering diet
13078	13AC.00	Diabetic weight reducing diet
13074	13B1.00	Diabetic diet
7045	14F4.00	H/O: Admission in last year for diabetes foot problem
22967	2BBF.00	Retinal abnormality - diabetes related
36855	2BBG.00	Retinal abnormality - non-diabetes
13100	2BBJ.00	O/E - no right diabetic retinopathy
13104	2BBK.00	O/E - no left diabetic retinopathy
47328	2BBk.00	O/E - right eye stable treated prolif diabetic retinopathy
9835	2BBL.00	O/E - diabetic maculopathy present both eyes
52041	2BBl.00	O/E - left eye stable treated prolif diabetic retinopathy
47144	2BBM.00	O/E - diabetic maculopathy absent both eyes
52630	2BBo.00	O/E - sight threatening diabetic retinopathy
11433	2BBP.00	O/E - right eye background diabetic retinopathy
11129	2BBQ.00	O/E - left eye background diabetic retinopathy
13099	2BBR.00	O/E - right eye preproliferative diabetic retinopathy
101881	2BBr.00	Impaired vision due to diabetic retinopathy
13103	2BBS.00	O/E - left eye preproliferative diabetic retinopathy
13097	2BBT.00	O/E - right eye proliferative diabetic retinopathy
13101	2BBV.00	O/E - left eye proliferative diabetic retinopathy
13102	2BBW.00	O/E - right eye diabetic maculopathy
13108	2BBX.00	O/E - left eye diabetic maculopathy

Medcode	Read code	Description
27921	2G51000	Foot abnormality - diabetes related
17095	2G5A.00	O/E - Right diabetic foot at risk
26664	2G5B.00	O/E - Left diabetic foot at risk
18056	2G5C.00	Foot abnormality - diabetes related
105740	2G5d.00	O/E - Left diabetic foot at increased risk
26666	2G5E.00	O/E - Right diabetic foot at low risk
105741	2G5e.00	O/E - Right diabetic foot at increased risk
31157	2G5F.00	O/E - Right diabetic foot at moderate risk
31171	2G5G.00	O/E - Right diabetic foot at high risk
35316	2G5H.00	O/E - Right diabetic foot - ulcerated
26667	2G5I.00	O/E - Left diabetic foot at low risk
31156	2G5J.00	O/E - Left diabetic foot at moderate risk
31172	2G5K.00	O/E - Left diabetic foot at high risk
35116	2G5L.00	O/E - Left diabetic foot - ulcerated
62384	2G5V.00	O/E - right chronic diabetic foot ulcer
49640	2G5W.00	O/E - left chronic diabetic foot ulcer
12703	3881.00	Education score - diabetes
34528	3882.00	Diabetes well being questionnaire
98954	3883.00	Diabetes treatment satisfaction questionnaire
107423	661N400	Diabetes self-management plan review
3550	66A..00	Diabetic monitoring
1684	66A4.00	Diabetic on oral treatment
8842	66A5.00	Diabetic on insulin
13069	66A8.00	Has seen dietician - diabetes
38078	66A9.00	Understands diet - diabetes
25636	66Aa.00	Diabetic diet - poor compliance
20696	66AA.11	Injection sites - diabetic
22823	66Ab.00	Diabetic foot examination
10977	66Ac.00	Diabetic peripheral neuropathy screening
13196	66AD.00	Fundoscopy - diabetic check
32619	66Af.00	Patient diabetes education review

Medcode	Read code	Description
53238	66AG.00	Diabetic drug side effects
16490	66AH.00	Diabetic treatment changed
107508	66AH200	Conversion to insulin by diabetes specialist nurse
13071	66AI.00	Diabetic - good control
28873	66Ai.00	Diabetic 6 month review
2378	66AJ.00	Diabetic - poor control
9013	66AJ.11	Unstable diabetes
22023	66AJz00	Diabetic - poor control NOS
43951	66AK.00	Diabetic - cooperative patient
66475	66Ak.00	Diabetic monitoring - lower risk albumin excretion
17869	66AL.00	Diabetic-uncooperative patient
61470	66Al.00	Diabetic monitoring - higher risk albumin excretion
17886	66AM.00	Diabetic - follow-up default
29041	66AN.00	Date diabetic treatment start
55123	66AO.00	Date diabetic treatment stopp.
12506	66AP.00	Diabetes: practice programme
12675	66AQ.00	Diabetes: shared care programme
95994	66Aq.00	Diabetic foot screen
100533	66AQ000	Unsuitable for diabetes year of care programme
101190	66AQ100	Declined consent for diabetes year of care programme
8836	66AR.00	Diabetes management plan given
6125	66AS.00	Diabetic annual review
101728	66As.00	Diabetic on subcutaneous treatment
107464	66AS000	Diabetes Year of Care annual review
18167	66AT.00	Annual diabetic blood test
101177	66At.00	Diabetic dietary review
12307	66AU.00	Diabetes care by hospital only
102434	66Au.00	Diabetic erectile dysfunction review
28769	66AV.00	Diabetic on insulin and oral treatment
102490	66Av.00	Diabetic assessment of erectile dysfunction
50175	66AW.00	Diabetic foot risk assessment

Medcode	Read code	Description
26604	66AY.00	Diabetic diet - good compliance
13057	679L.00	Health education - diabetes
100436	679L000	Education in self management of diabetes
107361	679L200	Education about diabetes and driving
107739	679L211	Advice about diabetes and driving
12682	679R.00	Patient offered diabetes structured education programme
104374	67D8.00	Provision of diabetes clinical summary
107560	67H9.00	Education about lifestyle for risk of diabetes
102767	67IJ100	Pre-conception advice for diabetes mellitus
18311	68A7.00	Diabetic retinopathy screening
19739	68A9.00	Diabetic retinopathy screening offered
61021	68AB.00	Diabetic digital retinopathy screening offered
11599	7276.00	Pan retinal photocoagulation for diabetes
61670	889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
47341	8A12.00	Diabetic crisis monitoring
24363	8A13.00	Diabetic stabilisation
11471	8B3l.00	Diabetes medication review
12213	8BL2.00	Patient on maximal tolerated therapy for diabetes
8414	8CA4100	Pt advised re diabetic diet
18066	8CE0.00	Diabetic leaflet given
105585	8CMW700	Diabetes clinical pathway
28856	8CP2.00	Transition of diabetes care options discussed
63412	8CR2.00	Diabetes clinical management plan
47032	8CS0.00	Diabetes care plan agreed
7059	8H2J.00	Admit diabetic emergency
35321	8H3O.00	Non-urgent diabetic admission
94330	8H4e.00	Referral to diabetes special interest general practitioner
7777	8H4F.00	Referral to diabetologist
12225	8H7C.00	Refer, diabetic liaison nurse
8306	8H7f.00	Referral to diabetes nurse
11677	8H7r.00	Refer to diabetic foot screener

Medcode	Read code	Description
11018	8HBG.00	Diabetic retinopathy 12 month review
18662	8HBH.00	Diabetic retinopathy 6 month review
47058	8Hg4.00	Discharged from care of diabetes specialist nurse
100422	8HgC.00	Discharged from diabetes shared care programme
57723	8HHy.00	Referral to diabetic register
47011	8Hj0.00	Referral to diabetes structured education programme
95641	8Hj1.00	Family/carer referral to diabetes structured education prog
93870	8Hj5.00	Referral to XPERT diabetes structured education programme
61557	8HKE.00	Diabetology D.V. requested
64142	8Hl1.00	Referral for diabetic retinopathy screening
82474	8Hl4.00	Referral to community diabetes specialist nurse
104287	8Hlc.00	Referral to community diabetes service
47370	8HLE.00	Diabetology D.V. done
72333	8HME.00	Listed for Diabetology admissn
50937	8HTe.00	Referral to diabetes preconception counselling clinic
105207	8HTE100	Referral to community diabetes clinic
69163	8HTi.00	Referral to multidisciplinary diabetic clinic
19381	8HTk.00	Referral to diabetic eye clinic
34541	8HVU.00	Private referral to diabetologist
18824	8I3W.00	Diabetic foot examination declined
12262	8I3X.00	Diabetic retinopathy screening refused
58639	8I57.00	Patient held diabetic record declined
18747	8I6F.00	Diabetic retinopathy screening not indicated
12247	8I6G.00	Diabetic foot examination not indicated
95094	8I81.00	Did not complete diabetes structured education programme
94956	8I84.00	Did not complete XPERT diabetes structured education program
107414	8I94.00	Diabetes structured education programme not available
101456	8IAs.00	Diabetic dietary review declined
103743	8IE2.00	Diabetes care plan declined
105937	8IEQ.00	Referral to community diabetes specialist nurse declined

Medcode	Read code	Description
106679	8OA3.00	Provision of written information about diabetes and driving
54419	918T.00	Diabetes key contact
52237	9360.00	Patient held diabetic record issued
57389	93C4.00	Patient consent given for addition to diabetic register
103798	9b92000	Diabetic medicine
28574	9h4..00	Exception reporting: diabetes quality indicators
11041	9h41.00	Excepted from diabetes qual indicators: Patient unsuitable
11348	9h42.00	Excepted from diabetes quality indicators: Informed dissent
101834	9h43.00	Excepted from diabetes qual indicators: service unavailable
106269	9m0..00	Diabetic retinopathy screening administrative status
61461	9M00.00	Informed consent for diabetes national audit
106332	9m00.00	Eligible for diabetic retinopathy screening
106441	9m01.00	Ineligible for diabetic retinopathy screening
106327	9m04.00	Excluded from diabetic retinopathy screening
106350	9m05.00	Excluded from diabetic retinopathy screening as moved away
106352	9m06.00	Excluded from diabetic retinopathy screening as deceased
106328	9m07.00	Excluded diabetc retinop screen as under care ophthalmolgist
106329	9m08.00	Excluded from diabetic retinopathy screening as blind
106218	9m0A.00	Declined diabetic retinopathy screening
106778	9m0C.00	Excluded frm diabetic retinopathy screen as terminal illness
107597	9m0D.00	Excluded from diabetic retinopthy screen as learn disability
106445	9m0E.00	Excluded from diabetic retinopathy screen physical disorder
44312	9M10.00	Informed dissent for diabetes national audit
38103	9N0m.00	Seen in diabetic nurse consultant clinic
32739	9N0n.00	Seen in community diabetes specialist clinic
38129	9N0o.00	Seen in community diabetic specialist nurse clinic
10824	9N1i.00	Seen in diabetic foot clinic
95813	9N1o.00	Seen in multidisciplinary diabetic clinic
2379	9N1Q.00	Seen in diabetic clinic
9974	9N1v.00	Seen in diabetic eye clinic
46521	9N2d.00	Seen by diabetologist

Medcode	Read code	Description
12507	9N2i.00	Seen by diabetic liaison nurse
9145	9N4I.00	DNA - Did not attend diabetic clinic
30648	9N4p.00	Did not attend diabetic retinopathy clinic
95553	9NiA.00	Did not attend diabetes structured education programme
94955	9NiE.00	Did not attend XPERT diabetes structured education programme
102768	9NiZ.00	Did not attend diabetes foot screening
97281	9Nl4.00	Seen by general practitioner special interest in diabetes
6430	9NM0.00	Attending diabetes clinic
54601	9NN8.00	Under care of diabetologist
11930	9NN9.00	Under care of diabetes specialist nurse
11094	9NND.00	Under care of diabetic foot screener
13191	9OL..11	Diabetes clinic administration
26605	9OLB.00	Attended diabetes structured education programme
51066	9OLC.00	Family/carer attended diabetes structured education prog
35383	9OLD.00	Diabetic patient unsuitable for digital retinal photography
94186	9OLF.00	Diabetes structured education programme completed
94011	9OLG.00	Attended XPERT diabetes structured education programme
93631	9OLL.00	XPERT diabetes structured education programme completed
93854	9OLM.00	Diabetes structured education programme declined
106738	9Oy0000	Diabetic foot screening invitation
106723	9Oy0200	Diabetic foot screening invitation first letter
106722	9Oy0300	Diabetic foot screening invitation second letter
107793	9Oy0400	Diabetic foot screening invitation third letter
711	C10..00	Diabetes mellitus
38986	C100.00	Diabetes mellitus with no mention of complication
14803	C100100	Diabetes mellitus, adult onset, no mention of complication
50972	C100z00	Diabetes mellitus NOS with no mention of complication
1682	C101.00	Diabetes mellitus with ketoacidosis
54856	C101100	Diabetes mellitus, adult onset, with ketoacidosis
38617	C101y00	Other specified diabetes mellitus with ketoacidosis

Medcode	Read code	Description
42505	C101z00	Diabetes mellitus NOS with ketoacidosis
21482	C102.00	Diabetes mellitus with hyperosmolar coma
43139	C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
72345	C102z00	Diabetes mellitus NOS with hyperosmolar coma
15690	C103.00	Diabetes mellitus with ketoacidotic coma
68843	C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
59288	C103y00	Other specified diabetes mellitus with coma
65062	C103z00	Diabetes mellitus NOS with ketoacidotic coma
16502	C104.00	Diabetes mellitus with renal manifestation
2475	C104.11	Diabetic nephropathy
35105	C104100	Diabetes mellitus, adult onset, with renal manifestation
13279	C104y00	Other specified diabetes mellitus with renal complications
35107	C104z00	Diabetes mellitus with nephropathy NOS
33254	C105.00	Diabetes mellitus with ophthalmic manifestation
41389	C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
47377	C105y00	Other specified diabetes mellitus with ophthalmic complicatn
34283	C105z00	Diabetes mellitus NOS with ophthalmic manifestation
16230	C106.00	Diabetes mellitus with neurological manifestation
59903	C106.11	Diabetic amyotrophy
7795	C106.12	Diabetes mellitus with neuropathy
16491	C106.13	Diabetes mellitus with polyneuropathy
39317	C106100	Diabetes mellitus, adult onset, + neurological manifestation
61523	C106y00	Other specified diabetes mellitus with neurological comps
22573	C106z00	Diabetes mellitus NOS with neurological manifestation
35399	C107.00	Diabetes mellitus with peripheral circulatory disorder
32403	C107.11	Diabetes mellitus with gangrene
32556	C107.12	Diabetes with gangrene
63357	C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
33807	C107200	Diabetes mellitus, adult with gangrene
65025	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
46290	C108y00	Other specified diabetes mellitus with multiple comps

Medcode	Read code	Description
64449	C108z00	Unspecified diabetes mellitus with multiple complications
33343	C10y.00	Diabetes mellitus with other specified manifestation
63371	C10y100	Diabetes mellitus, adult, + other specified manifestation
10098	C10yy00	Other specified diabetes mellitus with other spec comps
70821	C10yz00	Diabetes mellitus NOS with other specified manifestation
45491	C10z.00	Diabetes mellitus with unspecified complication
63762	C10z100	Diabetes mellitus, adult onset, + unspecified complication
64283	C10zy00	Other specified diabetes mellitus with unspecified comps
64357	C10zz00	Diabetes mellitus NOS with unspecified complication
52212	Cyu2.00	[X]Diabetes mellitus
41686	Cyu2000	[X]Other specified diabetes mellitus
100292	Cyu2300	[X]Unspecified diabetes mellitus with renal complications
17067	F171100	Autonomic neuropathy due to diabetes
44033	F345000	Diabetic mononeuritis multiplex
17247	F35z000	Diabetic mononeuritis NOS
31790	F372.00	Polyneuropathy in diabetes
5002	F372.11	Diabetic polyneuropathy
2342	F372.12	Diabetic neuropathy
48078	F372000	Acute painful diabetic neuropathy
35785	F372100	Chronic painful diabetic neuropathy
24571	F372200	Asymptomatic diabetic neuropathy
39420	F381300	Myasthenic syndrome due to diabetic amyotrophy
2340	F381311	Diabetic amyotrophy
37315	F3y0.00	Diabetic mononeuropathy
1323	F420.00	Diabetic retinopathy
7069	F420000	Background diabetic retinopathy
3286	F420100	Proliferative diabetic retinopathy
2986	F420200	Preproliferative diabetic retinopathy
10099	F420300	Advanced diabetic maculopathy
3837	F420400	Diabetic maculopathy
47584	F420500	Advanced diabetic retinal disease

Medcode	Read code	Description
10755	F420600	Non proliferative diabetic retinopathy
30477	F420700	High risk proliferative diabetic retinopathy
65463	F420800	High risk non proliferative diabetic retinopathy
11626	F420z00	Diabetic retinopathy NOS
17313	F440700	Diabetic iritis
10659	F464000	Diabetic cataract
34152	G73y000	Diabetic peripheral angiopathy
2471	K01x100	Nephrotic syndrome in diabetes mellitus
105302	K08yA00	Proteinuric diabetic nephropathy
107881	K08yA11	Clinical diabetic nephropathy
106360	K27y700	Erectile dysfunction due to diabetes mellitus
99628	Kyu0300	[X]Glomerular disorders in diabetes mellitus
55431	L180X00	Pre-existing diabetes mellitus, unspecified
7328	M037200	Cellulitis in diabetic foot
24327	M271000	Ischaemic ulcer diabetic foot
11663	M271100	Neuropathic diabetic ulcer - foot
9881	M271200	Mixed diabetic ulcer - foot
18142	N030000	Diabetic cheiroarthropathy
57333	N030011	Diabetic cheiropathy
27891	N030100	Diabetic Charcot arthropathy
53634	R054200	[D]Gangrene of toe in diabetic
31053	R054300	[D]Widespread diabetic foot gangrene
10642	ZC2C800	Dietary advice for diabetes mellitus
45250	ZL22500	Under care of diabetic liaison nurse
11977	ZL62500	Referral to diabetes nurse
13678	ZL62600	Referral to diabetic liaison nurse
8618	ZLA2500	Seen by diabetic liaison nurse
58133	ZLD7500	Discharge by diabetic liaison nurse
68546	ZRB4.00	Diabetes clinic satisfaction questionnaire
91164	ZRB4.11	CSQ - Diabetes clinic satisfaction questionnaire
94699	ZRB5.00	Diabetes treatment satisfaction questionnaire

Medcode	Read code	Description
68818	ZRB5.11	DTSQ - Diabetes treatment satisfaction questionnaire
38130	ZRB6.00	Diabetes wellbeing questionnaire
97824	ZRB6.11	DWBQ - Diabetes wellbeing questionnaire
67664	ZRBa.00	Education score - diabetes
16881	ZV65312	[V]Dietary counselling in diabetes mellitus
7563	66A3.00	Diabetic on diet only
49884	6761.00	Diabetic pre-pregnancy counselling
107603	C10P.00	Diabetes mellitus in remission
108993	661M400	Diabetes self-management plan agreed
109521	9m02.00	Eligibility temporarily inactive for diabetic retinop screen
109520	9m03.00	Eligibility permanently inactive for diabetic retinop screen
110056	9m0B.00	Excluded frm diab retinop screen as no currnt contct details
108634	9NJy.00	In-house diabetic foot screening
109133	L180700	Pre-existing malnutrition-related diabetes mellitus
Maturity onset diabetes of the young (MODY)		
14889	C100111	Maturity onset diabetes
31310	C108900	Insulin dependent diabetes maturity onset
63017	C108911	Type I diabetes mellitus maturity onset
97446	C108912	Type 1 diabetes mellitus maturity onset
43453	C10C.00	Diabetes mellitus autosomal dominant
46624	C10C.11	Maturity onset diabetes in youth
98392	C10C.12	Maturity onset diabetes in youth type 1
36695	C10D.00	Diabetes mellitus autosomal dominant type 2
59991	C10D.11	Maturity onset diabetes in youth type 2
40682	C10E900	Type 1 diabetes mellitus maturity onset
96235	C10E911	Type I diabetes mellitus maturity onset
97849	C10E912	Insulin dependent diabetes maturity onset
Latent autoimmune diabetes of adults (LADA)		
95636	C10ER00	Latent autoimmune diabetes mellitus in adult
Secondary diabetes		
52236	C10A.00	Malnutrition-related diabetes mellitus

Medcode	Read code	Description
66675	C10A000	Malnutrition-related diabetes mellitus with coma
33969	C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
100347	C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn
11551	C10B.00	Diabetes mellitus induced by steroids
26108	C10B000	Steroid induced diabetes mellitus without complication
51697	C10G.00	Secondary pancreatic diabetes mellitus
96506	C10G000	Secondary pancreatic diabetes mellitus without complication
61122	C10H.00	Diabetes mellitus induced by non-steroid drugs
67212	C10H000	DM induced by non-steroid drugs without complication
22487	C10N.00	Secondary diabetes mellitus
94383	C10N000	Secondary diabetes mellitus without complication
93380	C10N100	Cystic fibrosis related diabetes mellitus
32193	C11y000	Steroid induced diabetes
Other diabetes		
95539	C10FS00	Maternally inherited diabetes mellitus
2478	66AJ100	Brittle diabetes
68517	C10J.00	Insulin autoimmune syndrome
43857	C10M.00	Lipoatrophic diabetes mellitus
11848	C314.11	Renal diabetes
23479	C350011	Bronzed diabetes
110481	K081000	Acquired nephrogenic diabetes insipidus
Gestational Diabetes		
46577	66AX.00	Diabetes: shared care in pregnancy - diabetol and obstet
104588	66Ay.00	Gestational diabetes mellitus annual review
102435	8CE0000	Gestational diabetes information leaflet given
11359	L180.00	Diabetes mellitus during pregnancy/childbirth/puerperium
67635	L180000	Diabetes mellitus - unspec whether in pregnancy/puerperium
34639	L180100	Diabetes mellitus during pregnancy - baby delivered
49559	L180300	Diabetes mellitus during pregnancy - baby not yet delivered
96823	L180400	Diabetes mellitus in pueperium - baby previously delivered
10278	L180800	Diabetes mellitus arising in pregnancy

Medcode	Read code	Description
8446	L180811	Gestational diabetes mellitus
2664	L180900	Gestational diabetes mellitus
64384	L180z00	Diabetes mellitus in pregnancy/childbirth/puerperium NOS
108013	ZC2CB00	Dietary advice for gestational diabetes

ANNEX 5. BASELINE COVARIATES

Covariate
Number of patients
Number naïve new users
Number of mono, dual, or triple therapy
DEMOGRAPHICS
Age (at the index date)
Age category ≤ 18
Age category 18-35
Age category 36-49
Age category 50-64
Age category 65-74
Age category 75+
Sex
Calendar year of index date (baseline year)
Duration of look-back period
Time since first diagnosis of diabetes (when available)
LIFE STYLE FACTORS
Body mass index (BMI) (closest to index date; as available)
Blood pressure measurement (closest to index date; as available)
Smoking (closest to index date; as available)
Alcohol consumption (closest to index date; as available)
LABORATORY TESTS (closest to index date; as available)
HbA1c
Total cholesterol
HDL level
LDL level
Triglyceride level
eGFR
Creatinine
COMORBIDITIES (any available time prior to the index date)
Diabetes complications

Amputation
Diabetic ketoacidosis
Hypoglycemia
Diabetes with ophthalmic manifestations
Diabetes with neurological manifestations
Diabetes mellitus with peripheral circulatory disorders
Thyroid disorders
Hyperthyroidism
Hypothyroidism
Cancer
Cardiovascular
Hypertension
Atrial fibrillation / flutter
Heart failure
Stroke and Transient Ischemic Attack (TIA)
Myocardial infarction (MI)
Unstable Angina
Infections
Urinary tract infection
Pyelonephritis
Urosepsis (UTI following sepsis within 1 week)
Kidney disease
Acute renal disease
Chronic kidney disease
End-stage renal disease
Dialysis
Polycystic Ovary Syndrome (PCOS)

Obesity
Respiratory
Asthma
Chronic obstructive pulmonary disease (COPD)
pancreatitis
Bone disorders
Bone fracture
Osteoporosis
MEDICATIONS
Diabetes medications: prescriptions of other glucose-lowering drugs (oral or injected) (current use = up to 60 days before index date; past use = use any time prior to the index date)
Insulin
Non-insulin GLDs
Other non-diabetes medications: prescriptions of other medications (e.g. diuretics, antihypertensives, lipid-lowering, other cardiovascular medications etc.) (current use = up to and including 60 days before index date; past use = use any time prior to the 60 days before the index date)
CV medications
Cardiac Glycosides
Thiazides
Loop diuretics
Antiarrhythmics
Beta blocker
Vasodilator Antihypertensive Drug
Centrally Acting Antihypertensive Drugs
Alpha-adrenoceptor Blocking Drugs
Drugs affecting the renin-angiotensin system
Angiotensin Converting Enzyme (ACE) Inhibitors
Angiotensin II receptor blockers (ARB)
Renin Inhibitors

Other antihypertensives
Nitrates
Calcium channel blockers
Oral anticoagulants
Heparin and other low molecular weight heparins (LMWH)
Aspirin
Antiplatelet
Lipid-regulating Drugs
Bile Acid Sequestrants (lipid-regulating Drugs) - incl Colesevelam
Ezetimibe (only in combination w Statin)
Fibrates
Statins
Nicotinic Acid Group
Omega-3 Fatty Acid Compounds
Other lipid-regulating drugs
Oral Corticosteroids
Non-steroidal anti-inflammatory drugs
Psycholeptics
Antipsychotics
Antidepressants
Opiates
Anticonvulsants
Dopamine agonists
Agents for dementia

APPROVAL / SIGNATURE PAGE

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