Janssen Research & Development *

Study Protocol for Retrospective Observational Studies with Secondary Use of Data

Acute Pancreatitis in Patients with Type 2 Diabetes Who are New Users of Canagliflozin as Compared with New Users of Other Antihyperglycemic Agents: A Retrospective Cohort Study Using Large Claims Databases in the United States

JNJ-28431754-ZAE

Protocol RRA-21430

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Status: Approved
Date: 20 March 2018
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-ERI-135019923, 4.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

AHA	antihyperglycemic agents
CAD	coronary artery disease
CDM	Common Data Model
CV	cardiovascular
DM	diabetes mellitus
DPP-4(i)	dipeptidyl peptidase-4 (inhibitors)
EPS	exposure propensity score
GLP-1(a)	glucagon-like peptide-1 (agonists)
ICD-9	International classification of disease, version 9
IRB	Institutional Review Board
ITT	intent-to-treat
LADA	latent autoimmune diabetes in adults
OMOP	Observational Medical Outcomes Partnership
PVD	peripheral vascular disease
RLRM	regularized logistic regression model
SGLT2i	sodium-glucose co-transporter 2 (inhibitors)
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TZDs	thiazolidinediones
US	United States
ITT	Intent-to-treat
PP	Per protocol

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title: Acute Pancreatitis in Patients with Type 2 Diabetes Who are New Users of Canagliflozin as Compared with New Users of Other Antihyperglycemic Agents: A Retrospective Cohort Study Using Large Claims Databases in the United States

Rationale and Background: Diabetes mellitus (DM), a chronic condition, is associated with significant morbidity and mortality. Many comorbid conditions are prevalent in patients with type 2 diabetes mellitus (T2DM), including hypertension, obesity, hyperlipidemia, coronary artery disease (CAD), peripheral vascular disease (PVD), and renal dysfunction. In clinical trials of canagliflozin in patients with T2DM, acute pancreatitis cases have been reported infrequently. However, because acute pancreatitis is a relatively rare event and because patients with T2DM are known to be at increased risk of pancreatitis relative to non-T2DM patients, it is difficult to quantify the frequency of such events with precision and to determine whether there is a causal relationship with canagliflozin therapy simply based on clinical trials data. To address this knowledge gap and gain real-world evidence, we designed this observational study using large claims databases in the United States.

Research Question and Objectives: This study aims:

- To estimate the incidence rate of acute pancreatitis in patients with T2DM newly exposed to canagliflozin and comparator antihyperglycemic agents (AHAs, multiple comparators), based on both the overall crude and propensity-score matched cohorts, respectively.
- To compare the hazard of acute pancreatitis in patients with T2DM newly exposed to canagliflozin versus comparator AHAs (multiple comparators), based on propensity-score matched cohorts

Study Design: This is an observational, retrospective, new-user cohort study.

Population: The Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) version of 3 claims databases in the US (Truven MarketScan Commercial Claims and Encounters (CCAE), Truven MarketScan Medicare Supplemental (MDCR), and Optum Extended Socio-Economic (SES) databases) will be used for this study, which contains inpatient admission records, outpatient services, prescription drugs, eligibility status, and costs of services. Adult patients with T2DM who were newly exposed to a drug of interest (ie, canagliflozin or a comparator drug) between April 1, 2013 and the most recent database cutoff date at the time of the analysis will be eligible for the study. The date of first drug exposure will be considered the index date. Patients with a record of type 1 DM or secondary DM on or prior to the index date will be excluded from the analyses. In addition, patients must have at least one day follow-up after the index date to be eligible for the study.

The target exposure group of interest is canagliflozin.

Six classes of antihyperglycemic agents will be identified as the primary comparators for the study: 1) any new users of dipeptidyl peptidase-4 (DPP-4) inhibitors, 2) any new users of glucagon-like peptide-1 (GLP-1) agonists, 3) any new users of sulfonylureas, 4) any new users of thiazolidinediones (TZD), 5) any new users of insulin, and 6) any new users of other AHAs (excluding metformin). In addition, a total of 27 individual AHA therapies are identified as secondary comparators for this study, including: 1) DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin); 2) GLP-1 agonists (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide); 3) TZDs (pioglitazone, rosiglitazone, troglitazone); 4) sulfonylureas (glipizide, glyburide, glimepiride, chlorpropamide, tolazamide, tolbutamide, acetohexamide); 5) other AHAs (acarbose, bromocriptine, miglitol, nateglinide, repaglinide), and 6) SGLT2 inhibitors (dapagliflozin, empagliflozin). Therefore, a total of 33 formal statistical pairwise comparisons using propensity-score matched cohorts will be conducted. Metformin is often used as the first line therapy for managing T2DM, therefore, would not be included as a comparator group. The comparator group will be defined as new users of an AHA therapy with at least 365 days of prior observation during the April 1, 2013 to the most recent cutoff date at the time of the analysis.

Two cohorts will be created for each pairwise comparison: 1) canagliflozin, and 2) an AHA therapy, as identified above.

The outcome of interest will be the event of acute pancreatitis.

Variables: Definitions for the outcome, acute pancreatitis, were developed based on review of the literature, coding practice guideline documents, and consultation with clinical experts. Medication exposure codes were similarly identified through capture in the relevant therapeutic classification hierarchy and confirmed with clinical experts.

Data Source: The Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) version of 3 claims databases in the US, including Truven MarketScan Commercial Claims and Encounters (CCAE) database, Truven MarketScan Medicare Supplemental (MDCR) database, and Optum Extended SES databases, which contain inpatient admission records, outpatient services, prescription drugs, eligibility status, and costs of services.

Study Size: To detect a relative risk of 1.5 for acute pancreatitis, with a targeted type I error rate (alpha) of 0.05 (2-sided) and a type II error rate (beta) of 0.20 (power=80%), 191 acute pancreatitis events from both treatment groups combined would be needed. This would require a total matched sample size of approximately 118,000 patients (from both treatment groups, with 1:1 matching), assuming 1) the event rate of 1.0 per 1,000 person years in the comparison group, 2) the maximum duration of follow-up was 3 years, and 3) an annual drop-out rate of 15%. Note that these calculations reflect a general principle; the actual power to detect a certain level of risk would differ at the time of the analysis, since the baseline event rate, number of events, and duration of maximum follow-up would change accordingly and vary across databases.

As of June 2016 (approximately database cutoff date), nearly 106,000, 16,000, and 55,000 patients exposed to canagliflozin (new users) in the CCAE, MDCR, and Optum databases, respectively.

Data Analysis: For the exposure cohorts identified, an intent-to-treat (ITT) and a per protocol (PP, on-treatment) approach will be used for the analysis, respectively, with the PP analysis as the primary analytical approach. For the PP approach, only the events that occurred post-index date, while-on-treatment (plus 30 days of the last index medication prior to discontinuation) will be included in the analysis. Descriptive statistics will be presented, including number of persons exposed; time-at-risk; number of persons with an outcome during time-at-risk; incidence rate (number of persons with an outcome during time-at-risk / time-at-risk).

For comparative analysis, formal comparisons will be conducted using both ITT and PP approaches for new users of canagliflozin versus new users of an AHA therapy (as identified above), resulting in a total of 33 formal pairwise comparisons for each database (each pair individually matched using propensity-score method). A conditional Cox proportional hazards model based on time-to-first event approach, using propensity-score matched sets (with a variable matching), will be used to estimate the treatment effect size. Because multiple comparisons will be performed, we will apply Hochberg step-up procedure and report adjusted p-values (control for multiplicity), in addition to empirical p-values from the model. In addition, because of potential systematic bias associated with databases and observational studies, a set of negative control outcomes will be used to calibrate empirically observed p-values. Patients with a history of any form of pancreatitis will be evaluated and included in the study, if balance at baseline is achieved. However, if there is indication of imbalance at baseline, then patients with history of pancreatitis will be removed from the comparative analyses. The propensity score will be estimated through large-scale regularized regression, with demographics, all prior conditions/drugs/procedures, risk scores, utilization density as baseline covariates.

Milestones: The data extraction will start after the protocol is finalized. It is estimated that the analyses results are likely to be available in 6 to 8 weeks after the study protocol is finalized, and the study report is likely to be available in 6 to 8 weeks after the results are available. The results from this study will be evaluated for medical significance across functional teams and the external dissemination of the final results and publication plan will be consistent with Janssen internal policy.

5. STUDY MILESTONES

The key milestones of the study are highlighted below:

- The data extraction will start when the study protocol has been reviewed, finalized, and approved by relevant functional representatives.
- The study protocol will be finalized after all comments and questions from the PRAC reviewers being reconciled. All milestone dates (below) will be updated when the final study protocol is issued.
- The study results will be available approximately 6 to 8 weeks after the study protocol is finalized, and the study report is likely to be available in approximately 6 to 8 weeks after the results are available.
- The external dissemination of the final study results will be consistent with the Janssen publication policy.

Milestone	Planned date
Start of data collection	21 Mar 2018
End of data collection	16 May 2018
<Study progress report #>	N/A
<Interim report #>	N/A
Registration at EU PAS Register	16 Apr 2018
Final report of the study results	11 Jul 2018

6. RATIONALE AND BACKGROUND

Diabetes mellitus (DM), a chronic condition, is associated with significant morbidity and mortality. As the United States (US) population ages, the incidence rate and prevalence rate as well as its financial and social impact will continue to rise. Based on data from the National Diabetes Statistics Report (2014)[1], it was estimated that the overall prevalence of DM in the US population was 9.3% (29.1 million) in 2012, and reached a rate of 25.9% (11.8 million) among those 65 years and older. Patients with DM often have a high prevalence of several other comorbidities including hypertension, obesity, hyperlipidemia, coronary artery disease (CAD), peripheral vascular disease (PVD), and renal dysfunction.

The evidence from observational studies[2-5] suggests patients with T2DM are at increased risk (approximately 1.5- to 3-fold) of acute pancreatitis as compared with those without T2DM, and the variation of the effect estimate across those studies may reflect differences in the study design, patient population, and statistical methods used to control for confounding factors. In general, acute pancreatitis is uncommon in patients with T2DM, and the incidence rate ranged from 0.54 to 5.7 cases/1000 patient-years.

In addition, acute pancreatitis has been reported in clinical studies and postmarketing settings of incretin-based antihyperglycemic therapies (ie, DPP-4 inhibitors and GLP-1 agonists) for T2DM

and listed as safety events in the Summary of Product Characteristics (SmPCs).[6-11] Although there are warnings and precautions of the association of pancreatitis with these products in approved labeling (Annex 1), postmarketing studies[12-28] and meta-analyses of clinical trials[29-35] have yielded inconsistent results regarding an association. According to a recent assessment of this safety issue, the FDA and the EMA have not been able to confirm a causal relationship, and agree "that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data."[36]

In completed clinical trials of canagliflozin in patients with T2DM (data cut-off July 1, 2012), serious adverse events of pancreatitis (including acute pancreatitis) have been observed infrequently on canagliflozin (7 cases, 0.1%, [7/6,177]) and non-canagliflozin comparator (2 cases, 0.1%, [2/3262]), and the pooled incidence rates of serious pancreatitis from these clinical studies (0.87 and 0.50 per 1,000 person-years for canagliflozin and non-canagliflozin, respectively) are generally consistent with the rates of pancreatitis described in the peer reviewed medical literature. One additional serious case of pancreatitis associated with canagliflozin therapy was reported in a competed study (DIA3010) after this cut-off date. In addition, acute pancreatitis has also been reported based on spontaneous, postmarketing adverse event reporting, which is inherently limited by the lack of denominators or an appropriate comparison group. Because acute pancreatitis is a relatively rare event and because patients with T2DM are known to be at increased risk of pancreatitis relative to non-T2DM patients, it is difficult to quantify the frequency of such events with precision and to determine whether there is a causal relationship with canagliflozin therapy simply based on clinical trial data. To address this knowledge gap and gain real-world evidence, we designed this observational study using large claims databases in the United States.

7. RESEARCH QUESTION & OBJECTIVES

7.1. Research Question

The primary research questions include:

- What is the rate of acute pancreatitis in routine clinical practice among new users of canagliflozin and among new users of comparator antihyperglycemic agents (AHAs) (multiple comparators), based on both the overall crude and propensity-score matched cohorts, respectively?
- Is the hazard of acute pancreatitis increased among new users of canagliflozin relative to new users of comparator AHAs (multiple comparators) based on propensity-score matched cohorts?

7.2. Objectives

7.2.1. Primary Objective(s):

The primary objectives of the study are:

- To estimate the incidence rate of acute pancreatitis in patients with T2DM newly exposed to canagliflozin and comparator AHAs (multiple comparators), based on both the overall crude and propensity-score matched cohorts, respectively.
- To compare the hazard of acute pancreatitis in patients with T2DM newly exposed to canagliflozin versus comparator AHAs (multiple comparators), based on propensity-score matched cohorts

8. RESEARCH METHODS

8.1. Study Design

This is a retrospective, observational, new-user cohort study using large administrative claims databases in the US. Cohort studies allow direct estimation of incidence rates following exposures of interest, and the new-user design[37] can capture early events following treatment exposures while reducing confounding from previous treatment effects. New use allows for a clear exposure index date designation, but patients new to one drug or drug class can be prevalent users of other AHAs. Retrospective, observational studies using automated databases employ existing large datasets efficiently at lower resource costs, and typically in a more timely manner compared with prospective cohort creation with data collection and follow-up. Comparison across different therapeutic alternatives under the appropriate context can help inform treatment decisions and risk management.

The target exposure group of interest is canagliflozin, which was approved in the US on March 29, 2013. The study period extends from April 1, 2013 to the most recent database cutoff date at the time of the analysis). New users will be defined as patients whose first exposure to the drug occurs at least 365 days after their start of observation in the database (ie, at least 1 year baseline data, with the enrollment period starting on April 1, 2012). This enrollment criterion is imposed to ensure adequate capture of previous exposures to AHAs and of relevant past medical history, current comorbidities, and concomitant medications. The cohort start date (index date) will be defined by the date of first canagliflozin exposure in the study period, and the patient will be followed until the end of their individual observation.

Six groups of antihyperglycemic agents will be identified as the primary comparators for the study: 1) any new users of dipeptidyl peptidase-4 (DPP-4) inhibitors, 2) any new users of glucagon-like peptide-1 (GLP-1) agonists), 3) any new users of thiazolidinediones (TZDs), 4) any new users of insulin, 5) any new users of sulfonylureas, and 6) any new users of other AHAs (excluding metformin, since mainly first line therapy). In addition, Because the similarity of treatment effect for each substance within each class was untested, a total of 27 secondary comparator groups (ie, individual AHA therapy) will be established for this study as secondary comparisons, including new users of AHA medication from following classes: 1) DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin); 2) GLP-1 agonists (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide); 3) TZDs (pioglitazone, rosiglitazone, troglitazone); 4) sulfonylureas (glipizide, glyburide, glimepiride, chlorpropamide, tolazamide, tolbutamide, acetohexamide); 5) other AHAs (acarbose, bromocriptine, miglitol, nateglinide, repaglinide), and 6) SGLT2 inhibitors (dapagliflozin, empagliflozin). This will lead to a total of 33 pairwise formal statistical

comparisons, with each pair individually matched using treatment exposure propensity-scores. Metformin is often used as the first line therapy, therefore, will not be included as an independent comparator. Patients may take more than one antiglycemic agents, but per new user design, it must be the first time for a patient receiving an AHA therapy in the same class during the study period, although this patient might have been exposed to other AHAs in different classes.

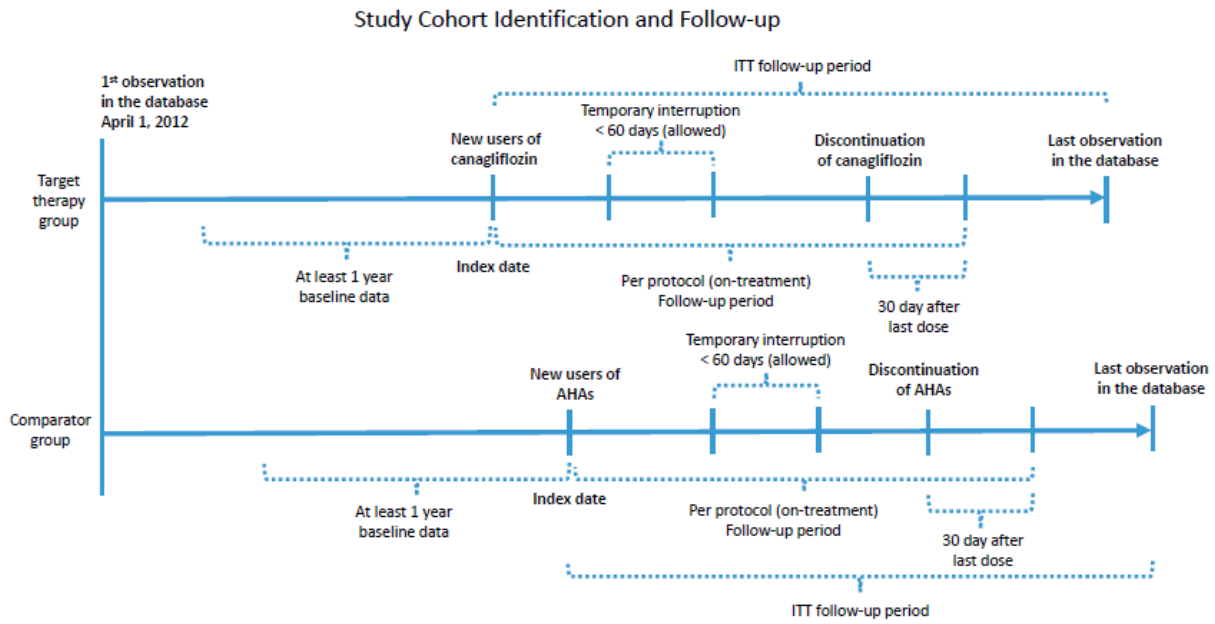
Patients with exposure to canagliflozin at any time in their observation will be excluded from the comparator group. The cohort start date will be defined by the date of first exposure to a comparator drug in the study period, and the patient will be followed until their cohort end date or the end of their individual observation. New users will be defined as patients whose first exposure to the drug occurs at least 365 days after their start of observation in the database (ie, at least 1 year baseline data, with the enrollment period starting on April 1, 2012).

For all cohorts, patients must have at least one diagnosis of T2DM prior to or on the cohort start date of index exposure, and must not have any diagnosis records for either type 1 diabetes mellitus (T1DM) or secondary diabetes at any time in the past medical history. In addition, patients must have at least one day follow-up after the index date to be eligible for the study.

The outcome of the study is the occurrence of acute pancreatitis, as defined by a hospital admission with a primary discharge diagnosis code of acute pancreatitis, based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM: 577.0).[39]

Two analytical strategies will be implemented for this study: ***intent-to-treat (ITT)*** and ***per protocol (PP, on-treatment)***. Since pancreatitis constitutes an acute event, the PP analysis will be considered the primary analytical approach. For the analysis using the ITT approach, patients will be followed from their cohort start date (as defined by first exposure) until the end of their observation time, regardless of whether they discontinue, switch or augment treatment. Acute pancreatitis episodes that occur during this time-at-risk will be considered as candidate events. This follow-up time analysis can be interpreted as an observational study analogue to the ***intent-to-treat (ITT)*** analysis in randomized clinical trials. For the analysis using the PP approach, acute pancreatitis episodes that occur during this time-at-risk while on the index treatment (plus 30 days of the last index medication, which is estimated based on outpatient pharmacy dispensing records) will be considered as candidate events. This follow-up time analysis can be interpreted as an observational study analogue to the ***per protocol (PP, on-treatment)*** analysis in randomized clinical trials. In contrast to the ITT approach, this type of PP analysis is intended to exclude events that might not be biologically related to the therapy of interest. Patients who switched from the index therapy to another medication will be censored at the time of switching plus 30 days (accounting for potentially biological window). Temporary interruption in therapeutic coverage (<= 60 days) is allowed and considered remained on therapy. However, any gap for therapeutic coverage > 60 days (calculated based on dispensing records) would be considered discontinuation of the therapy.

A study diagram outlining study cohort identification and follow-up is presented below.



The analysis will include a descriptive summary and a population-level estimation of the comparative effect. The descriptive summary will provide context for the number of persons and amount of follow-up time, and distribution of outcomes, incident rateobserved across the cohorts of interest. Specifically, for each of the 33 pairwise comparison cohorts (1: canagliflozin, 2: comparator AHA therapy), unadjusted (crude) incidence rate of acute pancreatitis will be estimated based on the number of persons with an acute pancreatitis episode observed during the time-at-risk, divided by the total follow-up time. These crude descriptive statistics will be presented for 2 sets of patient populations using both ITT and PP approaches: 1) overall cohorts, 2) propensity-score matched cohorts.

The population-level estimation analysis will compare canagliflozin new users to the new users of comparator AHA for the risk of acute pancreatitis based on propensity-score matched patient populations using both ITT and PP approaches. Unlike randomized clinical trials which determine treatment assignment, observational data reflect treatment choices made based on multiple factors, including insurance coverage, real-world practice patterns, medical history, and patient and physician preference. Because the comparison cohorts may vary by these baseline characteristics, confounding adjustment strategies must be employed to reduce the risk of systematic error that would bias the effect estimation. In this study, propensity score matching (with a variable ratio) will be used as an analytical device to identify the subset of individuals in each cohort who are comparable based on their baseline probability of treatment assignment. A conditional Cox proportional hazards model will be used to estimate the adjusted hazard ratio as a measure of relative risk of canagliflozin exposure versus comparator AHA exposure on the time-to-acute pancreatitis events. Because observational data may be inherent to systematic reporting or ascertainment biases, a set of negative control outcomes will be employed to calibrate the empirically observed p-values.

8.1.1. Selection of Comparators

The target exposure group of interest is canagliflozin. A total of 33 comparator AHA therapies are identified for this study.

While many AHAs are available to manage patients with T2DM, the frequency of use of these medications varies widely in clinical practice. Walker and colleagues[38] suggested that treatment pairs may be considered suitable for comparative effectiveness research, if at least half of the dispensings of each treatment-pair member fell within a preference range (ie, propensity score) of 30% to 70%. From that perspective, it is acknowledged that some of the treatment pairs in our study may not meet this definition, therefore, the comparative results should be interpreted in a proper context, despite that the analysis is based on propensity-score matched cohorts. In addition, if sample size is too small for a particular therapy, then that treatment arm may be removed from the comparative analyses and such a decision will be documented in the study report.

As mentioned previously, acute pancreatitis is listed as warnings and precautions in the SmPCs for incretin-based antiglycemic agents (DPP-4 inhibitors and GLP-1 agonists). However, the current evidence based on postmarketing studies[12-28] and clinical trials (as well as meta-analyses)[29-35] regarding incretin-based therapy and acute pancreatitis is neither consistent nor compelling, and the FDA and EMA agree that the causal relationship cannot be determined at this time.[36] However, if incretin-based drugs would indeed increase the risk of acute pancreatitis, the comparative analysis solely using these therapies as the comparator group would potentially mask safety concern associated with canagliflozin therapy. Therefore, the current study plans to include a comprehensive list of AHAs as comparators (multiple pairwise comparisons), with intent to provide the real-world evidence regarding any potential relationship between canagliflozin therapy and acute pancreatitis.

8.2. Setting and Study Population

8.2.1. Study Setting

The analysis will be conducted using 3 large claims databases in the U.S., including: 1) Truven MarketScan Commercial Claims and Encounters (CCAE) database, 2) Truven Health MarketScan Medicare Supplemental (MDCR) database, and Optum Extended SES database. A brief description of each database is listed below.

Truven MarketScan Commercial Claims and Encounters (CCAE) Database

The CCAE is a medical and drug insurance claims database with over 120 million unique de-identified patients that include active employees, early retirees, COBRA continuers, and their dependents insured by employer-sponsored plans. The database contains inpatient admission records, outpatient services, prescription drugs, eligibility status, and costs of services.

Truven MarketScan Medicare Supplemental (MDCR) Database The MDCR is an administrative health claims database for Medicare-eligible active and retired employees and their Medicare-eligible dependents from employer-sponsored supplemental plans (predominantly fee-for-service plans), with over 9 million unique de-identified patients. Only plans where both the Medicare-paid

amounts and the employer-paid amounts were available and evident on the claims were selected for this database. MDCR captures person-specific clinical utilization, expenditures, and enrollment across inpatient services, outpatient visits, prescription drug, and carve-out services. It also includes results for outpatient lab tests processed by large national lab vendors (but the actual lab results may not be available for most patients).

Optum Extended Socio-Economic (SES)

The Optum Extended SES database captures patient-level information for over 73 million unique de-identified patients, including race, ethnicity, clinical utilization, expenditures, and enrollment across inpatient services, outpatient visits, prescription drug, and carve-out services. Additionally, it includes results for outpatient lab tests processed by large national lab vendors (but the actual lab results may not be available for most patients). The Optum population is geographically diverse, spanning all 50 states. It is considered broadly representative of the US population enrolled in commercial health plans.

Data from these 3 databases have been standardized into the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM),[a] which includes a standard representation of health care experiences (such as information related to drug utilization and condition occurrence), as well as common vocabularies for coding clinical concepts and enables consistent application of analyses across multiple disparate data sources.

The following limitations of the databases should be noted:

- The commercially insured patients (eg, CCAE and Optum data) represent a higher socioeconomic status than the overall US population.
- Data are based on financial claims filed for reimbursement; disease coding may reflect financial incentives for reimbursement rather than clinically and systemically verified definitions.
- Prescriptions are those filled at outpatient pharmacies (and documented via prescription coverage), not those prescribed or administered within inpatient services. The extent to which prescribed records went unfulfilled is not known. It is also not known whether medications were actually taken as directed, although repeated dispensing of the same drug would suggest that this is the case.
- There is a data lag; data vendors only send records that are 100% paid, which can take about 6 months after year end.

8.2.2. Study Population

Adult patients (≥18 years of age) with T2DM, male or female, are considered eligible for this study. However, patients with age ≥65 years (CCAE data) and patients with age <65 (MDCR data) will be excluded from the study due to incomplete records or non-representative sample. Patients with any form of pancreatitis prior to or on the index date will be evaluated and included in the

[a] https://github.com/OHDSI/CommonDataModel

study, if balance at baseline is achieved after EPS matching (i.e., standardized difference < 10%). However, if there is evidence that such a balance was not achieved, patients with a history of pancreatitis would be removed from the comparative analyses, because such a history is an important predictor of future episodes.[2]

The definition for the study cohorts are further described below:

- First exposure to the particular drug in person's history
- The exposure start is between April 1, 2013 and the most recent database cutoff date at the time of the analysis). The study period ending date is the database cutoff date.
- At least 365 days of observation time prior to index
- At least 1 condition occurrence of 'Type II diabetes' any time before or on index
- Exactly 0 condition occurrences of 'Type I diabetes' any time before or on index
- Exactly 0 condition occurrences of 'Secondary diabetes' any time before or on index
- Have at least one day follow-up after the index date

As stated previously, the cohort definitions for each exposure classification (for each pairwise comparison) are as follows:

1. Canagliflozin new users
2. Comparator AHA new users
   - Qualifying drugs for the comparator includes 33 AHA therapies identified previously
   - Additional inclusion criteria:

   Exactly 0 drug exposures of canagliflozin any time before and any time after the index date.

These cohorts within each pairwise comparison will be created for 2 sets of patient populations: 1) overall, 2) propensity-score matched comparator cohorts

Concept set definitions, included concepts, and included source codes are included in Annex 2 for the following:

- Type II diabetes
- Type I diabetes
- Secondary diabetes

8.2.3. Subject Selection: Matching and Other Sampling Techniques

To compare acute pancreatitis incidence rate between new users of canagliflozin and new users of comparator AHAs (multiple comparators) in patients with similar baseline characteristics, each canagliflozin new user will be matched (with a variable ratio) to new users of comparator AHA based on estimated exposure propensity score (EPS), which would result in 33 sets of pairwise comparison cohorts. Large scale EPS will be estimated using regularized logistic regression models (RLRM) with the dependent variable being canagliflozin new user (yes vs no), and

independent variables including all potential baseline confounders available from the databases as candidate predictors, including demographics, baseline comorbidities and medications, as well as procedures.[40] Baseline variables will be evaluated based on claims data in the 12 months prior to exposure index date. To avoid over-fitting models and to accommodate a large number of predictors, the RLRM will be fit using a cyclic coordinate descending (CCD) method with L1 penalty (ie, least absolute shrinkage and selection operator [LASSO]).[41] The optimal regularization hyper-parameters will be estimated using 10-fold cross-validation, with a starting variance of 0.01 and a tolerance of 2e-7. Conventional greedy algorithms with nearest neighbor matching minimizing the absolute difference between EPS will be used for matching.[42] This algorithm in general achieves a global or close-to-global optimum. Empirical distribution of the estimated EPS will be plotted according to the index AHA exposure groups. Maximum matching caliper of the propensity score (on the logit scale) will be 20% of the standard deviation of the logit of the propensity scores.[43] Standardized differences will be tabulated across potential confounders to evaluate the matching effectiveness in achieving baseline covariate balance.[47]

In addition to EPS matching strategy, EPS stratification method will also be used as complementary approach. The canagliflozin cohort and comparator cohort will be stratified into 5 quantiles of the EPS distribution. The comparative analyses will be carried out using a conditional Cox proportional hazards model, using the EPS strata as the matched sets. Propensity score stratification adjustment strategy will preserve a larger sample as compared with a variable matching or one-to-one matching. The balance of baseline covariates will be evaluated prior to formal analyses.

Particular attention will be paid to examine the balance of pancreatic diseases between the comparison groups, since there is evidence suggesting that those factors are associated with significantly elevated risk of acute pancreatitis in patients with T2DM.[5] It is intended that these factors will be well balanced prior to executing the comparative analysis based on conditional Cox proportional hazards model.

8.3. Variables

8.3.1. Variables for Analytical Studies

8.3.1.1. Exposure

All exposure cohorts are defined in Section 8.2.2. The cohort start date is defined as the first date of exposure (ie, the beginning of time-at-risk) to the index drug. The cohort end date (the end of time-at-risk) will vary depending on the ITT or PP approach.

For the analysis based on the **ITT approach**, the cohort end date is the date of the event for patients who experienced acute pancreatitis (ie, censored at the first event date), whereas the cohort end date is the earliest of the end of enrollment, lost to follow-up, or the end of observation period for patients who did not experience acute pancreatitis (regardless of whether the patient switches to

another AHA or not). Acute pancreatitis cases that occurred during the entire study period (post-index date) are eligible for analyses.

For the analysis based on the **PP approach (on-treatment)**, the cohort end date is the date of the first event (that is considered while-on-treatment, as described further below) for patients who experienced acute pancreatitis (ie, censored at the first event date), whereas the cohort end date is the earliest of discontinuation of therapy, the end of enrollment, lost to follow-up, or the end of observation period for patients who did not experience acute pancreatitis. The therapeutic coverage is imputed based on outpatient pharmacy dispensing records. Temporary interruption (ie, <= 60 days) in therapeutic coverage is allowed and considered remained on therapy. A patient is considered discontinued therapy, if the therapeutic coverage gap is > 60 days between two consecutive dispensings. Acute pancreatitis cases are considered eligible for analyses, if they occurred on-treatment (post-index date) or within 30 days of the last medication (ie, the end of the treatment) during the observation period (as a conservative approach).

8.3.1.2. Baseline Covariates for Propensity Score Model

Propensity scores will be used as an analytic strategy to reduce potential confounding due to imbalance in baseline covariates between the target and comparator cohorts. The propensity score is the probability of a patient being classified in the target cohort vs. the comparator cohort, given a set of observed covariates.

The types of baseline covariates used to fit the propensity score model will be:

- Demographics
    - Gender
    - Age group (5-year bands)
    - Index year
    - Index month
- Record of comorbidities during up to 365 days prior to or on the start date of comparative cohorts
- Record of relevant drug exposure during up to 365 days prior to or on the start date of comparative cohorts
- Record of interventional or diagnostic procedures during up to 365 days prior to or on the start of comparative cohorts
- Record of clinical findings and tests during up to 365 days prior to or on the start date of comparative cohorts
- Charlson Index - Romano adaptation, using comorbidities at any time prior to or on the start date of comparative cohorts
- Number of distinct comorbidities observed within 365 days prior to or on the start date of comparative cohorts
- Number of distinct drug exposures observed within 365 days prior to or on the start date of comparative cohorts
- Number of distinct interventional or diagnostic procedures observed within 365 days prior to or on the start date of comparative cohorts

- Number of distinct clinical findings observed within 365 days prior to or on the start date of comparative cohorts
- Number of distinct clinical tests observed within 365 days prior to or on the start date of comparative cohorts
- Number of outpatient office visits observed within 365 days prior to or on the start date of comparative cohorts
- Number of inpatient visits observed within 365 days prior to or on the start date of comparative cohorts
- Number of emergency room visits observed within 365 days prior to or on the start date of comparative cohorts
- Number of prescriptions for antiglycaemic medication observed within 365 days prior to or on the start date of comparative cohorts

Specific drug exposures that are used to define the target and comparator cohorts will be excluded from the propensity score model fitting, but will be presented for clinical characterization.

8.3.1.3. Outcome

The outcome cohort definition for acute pancreatitis will include people who were admitted to the hospital with a discharge diagnosis of ICD-9 code 577.0, which appeared to have the best positive predictive value (PPV) and specificity based on prior studies.[39]

Considerations for the outcome definition:

- Acute pancreatitis may occur multiple times for a given subject. However, for the incidence rate calculation and model-based statistical comparisons, only the first event will be used for the analysis. As described above, the determination of the time-at-risk is consistent with this analytical strategy.

8.3.1.4. Baseline Characteristics and Variables for Descriptive Analysis

From the model performance perspective, the balance of baseline characteristics will be assessed before and after matching for all the propensity-score models. In addition, some key baseline characteristics will also be evaluated to understand clinical characteristics of the study population, including (as an example, but may not be limited to):

Baseline AHA treatment (these medication classes may not be mutually exclusive) prior to the index date.

- Metformin (any)
- Metformin plus ≥1 AHAs
- DPP-4
- GLP-1
- TZDs
- Sulfonylureas

- Insulin
- Other AHA
- Number of baseline AHA therapies

Baseline demographics:

- Sex: Sex is a dichotomous variable (male=1, female=0)
- Age: Age in years will be determined on the index date.
  - Continuous variable
  - Predefined age groups also will be established
- Index year: The year of a patient's index date

Baseline comorbid conditions: Comorbid conditions will be identified by ≥1 ICD-9 diagnosis code in any position during the pre-index period. The comorbid conditions of interest are outlined below:

- Atrial fibrillation
- Congestive heart failure
- Cardiomyopathy
- Coronary artery disease
- COPD
- Dementia
- Diabetes
- Hemiplegia or Paraplegia
- Mild liver disease
- Moderate or severe liver disease
- HIV
- Hyperlipidemia
- Hypertension
- Stroke
- Transient ischemic attack (TIA)
- Malignancy
- Myocardial Infarction
- Peptic ulcer disease
- Peripheral vascular disease
- Renal disease

    - End stage renal disease
- Rheumatic disease
- Venous thromboembolism
- Biliary disease
- Pancreatitis
    - Acute
    - Chronic
- Other pancreatic disease
- Alcoholism
- Obesity
- Cholelithiasis
- Cholecystitis
- Autoimmune disease (e.g., Sjögren syndrome)
- Hypercalcemia
- Cholecystectomy
- Trauma (including iatrogenic damage, such as ERCP)
- Baseline Charlson Comorbidity Index (CCI) score: Based on pre-index period healthcare encounters.

Baseline medication usage (non-AHA): Medication dispensing records will be identified during the 1-year pre-index period for all medications within each of the following drug classes. Patients with ≥1 medication dispensing will be flagged in the respective drug group. Study team will determine if a minimum duration of exposure is required for one or all of these medications.

- Angiotensin-converting-enzyme (ACE) inhibitors
- Angiotensin Receptor Blockers (ARBs)
- Antiarrhythmic drugs
- Beta-blockers
- Calcium channel blockers
- Digoxin
- Diuretics (non-loop)
- Loop diuretics
- Statins or ezetimibe
- Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
- Anticoagulants

- Azathioprine
- Glucocorticoids,
- Valproic acid
- Oral contraceptives (hormone replacement therapy: HRT)
- Antiretroviral agents for HAART (highly active antiretroviral therapy)

In addition, mean follow-up time (PP and ITT) of patients in each database will be described.

8.4. Data Sources

This study will utilize 3 claims databases in the US, previously described in Section 8.2.1.

8.5. Sample Size and Study Power

The table below presents the total number of events and sample sizes (EAST 6.2 User Manual. 2013, Cytel Inc.) needed to detect a relative increase in risk of acute pancreatitis, which might be associated with canagliflozin therapy, for a range of potential values of baseline risk in the comparator AHA group. As expected, as the baseline event rate decreases, the required sample size increases, although the total number of events needed to detect a certain level of risk (eg, hazard ratio) remains the same. For example, to detect a relative risk of 1.5 for acute pancreatitis, with a targeted type I error rate (alpha) of 0.05 (2-sided) and a type II error rate (beta) of 0.20 (power=80%), 191 acute pancreatitis events from both treatment groups combined would be needed. This would require a total matched sample size of approximately 118,000 patients (from both treatment groups, with 1:1 matching), assuming the event rate of 1.0 per 1,000 person years in the comparison group, the maximum duration of follow-up was 3.0 years and an annual drop-out rate of 15%. Note that these calculations reflect a general principle; the actual power to detect a certain level of risk would be changing at the time of each analysis, since the baseline event rate, number of events, and duration of maximum follow-up would change accordingly.

1-Sided Alpha	Power	Relative Risk increase	Incidence Rate of Control Group (per 1000 PYs)	Total Number of Events Needed*	Estimated Total Number of Subjects (1:1 matching)*	Estimated Total Number of Subjects (1:1 matching)**
0.025	80%	50% (RR=1.5)	1.0	191	90752	117844
			1.5	191	60544	78610
		75% (RR=1.75)	1.0	101	43635	56660
			1.5	101	29114	37799
		100% (RR=2.0)	1.0	66	26144	33946
			1.5	66	17445	22648
	90%	50% (RR=1.5)	1.0	256	121636	157948
			1.5	256	81148	105362
		75% (RR=1.75)	1.0	135	58324	75734
			1.5	135	38914	50524
		100% (RR=2.0)	1.0	88	34858	45261
			1.5	88	23260	30198

*Assuming 3 years of enrollment and 3.25 years of maximum duration of follow up adjusting for 15% annual drop-out rate.
**Assuming maximum duration of 3 years
Sample size was calculated using the EAST software (EAST 6.2 User Manual. 2013, Cytel Inc).

Based on preliminary feasibility assessment, as of June 2016 (approximately the current database cutoff date), approximately 106,000, 16,000, and 55,000 patients exposed to canagliflozin (new users) based on the CCAE, MDCR, and Optum databases, respectively.

8.6. Data Management and Data Preparation

All data will be maintained in the Microsoft Analytics Platform System (APS) database appliance. All analyses will be conducted against the CCAE database that has been standardized to the OMOP CDM version 5. Analyses will be performed in SQL and R. The primary investigator and sponsor will be blinded to the results of any study comparisons for decisions needed to resolve any unanticipated analytical or data issues.

8.7. Data Analysis

8.7.1. Descriptive Summary

For each of the study cohorts defined (overall, propensity-score matched pairwise comparison cohorts), the following statistics will be calculated:

- Number of persons exposed
- Time-at-risk (days observed in ITT and PP approach)
- Number of persons with an outcome during time-at-risk
- Incidence rate = Number of persons with an outcome during time-at-risk / Time-at-risk and its 95% CIs

Considerations for descriptive summary:

- These incidence rates provide context for frequency of new events with a population.
- The rates between cohorts should not be directly compared, as crude rate ratios can be biased. If formal comparisons between cohorts are required, a full comparative analysis should be conducted to estimate adjusted relative risk and used for comparison as described below.

Descriptive statistics will also be summarized for a set of baseline characteristics identified for this study (Section 8.3.1.4). Descriptive statistics for categorical variables (eg, frequencies and proportions) and continuous variables (eg, minimum, maximum, median, mean and standard deviation) will be presented accordingly by each treatment cohort including 1) overall cohorts (non-matched): canagliflozin new users vs. comparator AHA new users, 2) Pairwise comparison cohorts (propensity-score matched): canagliflozin new users vs. comparator new users. The standardized difference after propensity-score matching will also be presented.

Several mock tables outlining output of the descriptive results are presented in Annex 2. These tables are presented as examples, and actual presentation (eg, format) could be different.

8.7.2. Population-level Estimation

This analysis will involve a total of 33 sets of formal pairwise comparisons based on propensity-score matched cohorts using the **ITT** and **PP** approach, respectively.

The primary analysis will compare canagliflozin with 6 classes of AHA therapies including 1) DPP-4 inhibitors, 2) GLP-1 agonists, 3) TZDs, 4) sulfonylureas, 5) insulin, 6) other AHAs (excluding metformin). The secondary analysis will compare canagliflozin with 27 individual substance within classes, including 7) alogliptin, 8) linagliptin, 9) saxagliptin, 10) sitagliptin, 11) vildagliptin as DPP-4 inhibitors; 12) albiglutide, 13) dulaglutide, 14) exenatide, 15) liraglutide, 16) lixisenatide as GLP-1 agonists; 17) pioglitazone, 18) rosiglitazone, 19) troglitazone as TZDs; 20) glipizide, 21) glyburide, 22) glimepiride, 23) chlorpropamide, 24) tolazamide, 25) tolbutamide, 26) acetohexamide as sulfonylureas; 27) acarbose, 28) bromocriptine, 29) miglitol, 30) nateglinide, 31) repaglinide as other AHAs; and 32) dapagliflozin, and 33) empagliflozin as other SGLT2 inhibitors.

A conditional Cox proportional hazards model based on time-to-first event approach, using propensity-score matched sets will be used for the statistical analysis. The propensity score will be estimated through large-scale regularized regression, with demographics, all prior conditions/drugs/procedures, risk scores, utilization density as baseline covariates as described in Section 8.2.3.

In total, 33 overall comparisons * 1 outcome * 2 time-at-risk windows (ITT or PP) * 2 adjustment strategies (variable PS matching or PS stratification) * 3 databases = 396 (potential) comparative analyses will be performed (subject to first passing the study diagnostics, Annex 3).

Because multiple comparisons will be performed, Hochberg step-up procedure (which is less conservative than the Bonferroni correction) will be used to report adjusted p-values controlling for multiplicity.44 In addition, because of potential systematic bias associated with observational studies, a set of negative control outcomes (see Annex 2) will be used to calibrate empirically observed p-values.[45,46]. It is worth noting that given the large number of comparisons being carried out, the safety results should be interpreted in the context of totality of evidence, including effect size estimates, 95% CIs, negative controls, consistency and robustness across multiple data sources and numerous sensitivity analyses.

Model diagnostics will be generated and will include propensity score distribution, covariate balance, and empirical null from negative control outcomes. Covariate balance statistics will be evaluated before and after propensity matching to ensure adequate comparability between cohorts has been achieved, overall and with specific focus on key baseline characteristics previously discussed. Final results will include the hazard ratio, 95% confidence interval, and p-value (pre- and post-empirical calibration, and multiplicity-adjusted). A Kaplan-Meier plot will be generated to visualize the time-to-event attrition in the comparison cohorts.

Several mock tables outlining output of the formal comparative results are presented in Annex 2. These tables are presented as examples and actual presentation (eg, format) could be different.

8.7.3. Sensitivity analyses

Several sensitivity analyses will be conducted to assess the robustness of the study findings for the 6 primary comparisons based on separate EPS matched cohorts. Of note, in some pre-specified subgroups with small number of eligible patients, PS matching may be unsatisfactory, as a result the risk parameter estimates may not be reliable. We will evaluate PS matching before the subgroup sensitivity analysis. If model diagnostics show unbalanced comparative cohorts, the comparative estimates based on the cohorts that are PS-matched will be generated. Such circumstances will be documented in the study report with the understanding that when the performance of PS matching is not satisfactory, the results need to be interpreted with caution due to potential bias and confounding.

- Metformin-add-on therapy: We will compare new users of canagliflozin with new users of other AHAs as metformin-add-on therapies only
- We will conduct separate analysis for patients with and without prior history of pancreatitis
- We will perform PS matching using a different caliper of 10% of the standard deviation of the logit of propensity scores
- For the on-treatment (per protocol) analysis, we will repeat analysis using 0 and 60 days after the last index medication use as biological window of drug exposure.

For sensitivity analyses, in total, 6 primary comparisons * [metformin-add-on (1) + history of pancreatitis (2) + residual effect (2)] * 1 outcome * 2 time-at-risk windows (ITT or PP) * 2 adjustment strategies (variable matching or PS stratification) * 3 databases + 6 primary comparisons * different matching caliper (1) * 1 outcome * 2 time-at-risk windows (ITT or PP) * 3 databases = 396 (potential) comparative analyses will be performed (subject to first passing the study diagnostics, Annex 3).

8.8. Quality Control

All analyses will be performed within the Epidemiology Analytics team. A lead programmer will develop and execute the source code. A second programmer will review the code and execute to confirm the results generated. Analysis source code will be provided as part of the final output generated.

8.9. Strengths and Limitations of the Research Methods

8.9.1. Strengths

- The CCAE database provides context by examining the real-world experience of a large number of patients exposed to SGLT2i and non-SGLT2i AHA treatments.

- Cohort studies allow direct estimation of incidence rates following exposure of interest, and the new-user design[37] can capture early events following treatment exposures while avoiding confounding from previous treatment effects. New use allows for a clear exposure index date designation but patients new to one drug or drug class can be prevalent users of other AHAs.
- EPS matching allows balancing on a large number of baseline potential confounders. [47]

8.9.2. Limitations

- Misclassification among different types of diabetes is possible as a result of misdiagnosis and/or inaccurate coding. For example, (i) latent autoimmune diabetes in adults (LADA; an autoimmune form of T1DM presenting in adulthood) is often initially misdiagnosed and treated with oral AHAs.[48]
- The definition for T2DM relies on ICD-9 codes taken at face value, and some patients with bona fide autoimmune diabetes may still remain, despite our best attempt to exclude them. For example, it is possible that some patients with T1DM who are older than 40 years of age are correctly recognized as T1DM by their treating healthcare providers, yet their insurance claims captured during entire enrollment history never use codes for T1DM. Some patients with T1DM may take insulin together with oral AHAs, including metformin[49] DPP-4i,[50] GLP-1,[51] canagliflozin,[52] etc.
- Patients with T2DM who were not managed by any AHAs were not included. Some of these patients may be newly diagnosed with T2DM and managed by diet and exercise, and may not be comparable to the study population of interest for this study.
- Causality between drug exposure and acute pancreatitis cannot be drawn for individual cases. The results from this study should be interpreted in the context of data from other sources, including clinical trials and other observational studies.
- While this study is restricted to patients who must have at least 1 year observable data prior to the index date, some patients might have had a history of pancreatitis beyond this time period and such a record may not be captured in the database.
-
- Socioeconomic variables (such as race/ethnicity, education, income), behavioral variables (such as diet, alcohol consumption, eating disorders) are not available or may not be completely captured from these databases, which will lower the validity for risk factor/confounding adjustment, or causal interpretation.
- Free drug samples are not captured in insurance claims databases, which may result in misclassification of some exposure as non-exposure, prevalent drug use as new use (potentially missing incident events or incident events following exposure misclassified as historical events). Although some Health Maintenance Organizations (HMOs) forbid direct access to sales representatives and therefore may not have the free-sample issue, sensitivity analyses are not done due to limited sample size and changing of insurance over time.
- In the US, different dosage forms of the SGLT2i drugs are sold at the same price. It is possible for patients to fill the high dosage form prescriptions but actually take low doses by splitting pills. This will not influence estimated cumulative dosage but could misclassify the high versus low dosage form.

- Large-scale propensity score may not completely remove confounding bias. [11] For example, some variables may only be associated with exposure but not acute pancreatitis; disease severity and inherent acute pancreatitis risk at baseline is not directly measurable, and there is in general lack of data on behavioral and lifestyle data, genetics or ethnicity in claims databases.

9. PROTECTION OF HUMAN SUBJECTS

- The use of Truven CCAE database was reviewed by the New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project uses only de-identified data and would not involve human subjects.
- Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians. At no time during the study will the sponsor receive patient-identifying information.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS AND ADVERSE REACTIONS

This study uses coded data that already exist in an electronic database. In this type of database, it is not possible to link (ie, identify a potential causal association between) a particular product and medical event for any individual. Thus, the *minimum criteria for reporting an adverse event (ie, identifiable patient, identifiable reporter, a suspect product, and event) are not available* and adverse events are not reportable as individual adverse event reports. The study results will be assessed for medically important results.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Publication of the study results is planned upon quality checking, team review and approval. If it is determined that there is insufficient power upon review of the results from the proposed analysis, publication may be delayed until subsequent analyses with increased power from exposures accumulated on subsequent data refreshes can be performed.

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ANNEX 1. ANTIHYPERGLYCEMIC AGENTS AND APPROVED EU SMPC TEXT ON ACUTE PANCREATITIS

Class	Product	Section 4.4 Warnings and Precautions	Section 4.8 Adverse Reactions
DPP-4	Vipidia (alogliptin benzoate)	Acute pancreatitis Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. In a pooled analysis of the data from 13 studies, the overall rates of pancreatitis reports in patients treated with 25 mg alogliptin, 12.5 mg alogliptin, active control or placebo were 2, 1, 1 or 0 events per 1,000 patient years, respectively. In the cardiovascular outcomes study the rates of pancreatitis reports in patients treated with alogliptin or placebo were 3 or 2 events per 1,000 patient years, respectively. There have been spontaneously reported adverse reactions of acute pancreatitis in the post-marketing setting. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain, which may radiate to the back. If pancreatitis is suspected, Vipidia should be discontinued; if acute pancreatitis is confirmed, Vipidia should not be restarted. Caution should be exercised in patients with a history of pancreatitis.	Acute pancreatitis is listed with a frequency of 'Not known'.
DPP-4	Trajenta (linagliptin)	Acute pancreatitis Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. In post-marketing experience of linagliptin there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Trajenta should be discontinued; if acute pancreatitis is confirmed, Trajenta should not be restarted. Caution should be exercised in patients with a history of pancreatitis.	Pancreatitis was reported more often in patients randomized to linagliptin (7 events in 6,580 patients receiving linagliptin versus 2 events in 4,383 patients receiving placebo). Pancreatitis is listed with a frequency of 'Not known' for monotherapy and in combination with metformin, and with sulphonylurea or empagiflozin. Pancreatitis is listed with a frequency of 'Uncommon' in combination with insulin.

Class	Product	Section 4.4 Warnings and Precautions	Section 4.8 Adverse Reactions
DPP-4	Onglyza (saxagliptin hydrochloride)	Acute pancreatitis Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis; persistent, severe abdominal pain. If pancreatitis is suspected, Onglyza should be discontinued; if acute pancreatitis is confirmed, Onglyza should not be restarted. Caution should be exercised in patients with a history of pancreatitis. In post-marketing experience of saxagliptin, there have been spontaneously reported adverse reactions of acute pancreatitis.	Pancreatitis is listed with a frequency of 'Uncommon' in monotherapy and in combination with metformin, sulphonylurea or thiazolidinedione, with a footnote 'Adverse reaction originates from saxagliptin or dapagliflozin post-marketing surveillance data'. SAVOR trial results The incidence of adjudicated pancreatitis events was 0.3% in both Onglyza-treated patients and placebo-treated patients in the intent-to-treat population
DPP-4	Januvia (sitagliptin phosphate monohydrate)	Acute pancreatitis Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of sitagliptin (with or without supportive treatment), but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, Januvia and other potentially suspect medicinal products should be discontinued; if acute pancreatitis is confirmed, Januvia should not be restarted. Caution should be exercised in patients with a history of pancreatitis.	Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported. Acute pancreatitis and fatal and non-fatal haemorrhagic and necrotizing pancreatitis are listed with a frequency of 'Not known', with the footnotes 'Adverse reactions were identified through postmarketing surveillance: See section 4: See TECOS Cardiovascular Safety Study below'. TECOS Cardiovascular Safety Study The incidence of adjudication-confirmed pancreatitis events was 0.3 % in sitagliptin-treated patients and 0.2 % in placebo-treated patients.
DPP-4	Galvus (vildagliptin)	Acute pancreatitis Use of vildagliptin has been associated with a risk of developing acute pancreatitis. Patients should be	Pancreatitis is listed with a frequency of 'Not known' in a post-marketing AR table.

Class	Product	Section 4.4 Warnings and Precautions	Section 4.8 Adverse Reactions
		informed of the characteristic symptom of acute pancreatitis. If pancreatitis is suspected, vildagliptin should be discontinued; if acute pancreatitis is confirmed, vildagliptin should not be restarted. Caution should be exercised in patients with a history of acute pancreatitis.	
GLP-1	Eperzan (albiglutide)	<u>Acute pancreatitis</u> Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis. In clinical trials, acute pancreatitis has been reported in association with Eperzan (see section 4.8). Patients should be informed of the characteristic symptom of acute pancreatitis. If pancreatitis is suspected, Eperzan should be discontinued; if pancreatitis is confirmed, Eperzan should not be restarted. Caution should be exercised in patients with a history of pancreatitis.	The most serious adverse reaction in clinical trials was acute pancreatitis (see section 4.4). Pancreatitis is listed with a frequency of 'Uncommon'. The incidence of pancreatitis (adjudicated as likely to be related to therapy) in the clinical studies was 0.3% for Eperzan compared to 0% for placebo and 0.1% for comparators (i.e. liraglutide, pioglitazone, glimepiride, sitagliptin, and insulin glargine) with or without additional background antidiabetic therapy (e.g. metformin).
GLP-1	Trulicity (dulaglutide)	<u>Acute pancreatitis</u> Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis. In clinical trials, acute pancreatitis has been reported in association with dulaglutide (see section 4.8). Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, dulaglutide should be discontinued. If pancreatitis is confirmed, dulaglutide should not be restarted. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis (see section 4.8).	Acute pancreatitis is listed with a frequency of 'Rare'. <u>Acute pancreatitis</u> The incidence of acute pancreatitis in phase II and III clinical studies was 0.07% for dulaglutide compared to 0.14% for placebo and 0.19% for comparators with or without additional background antidiabetic therapy. <u>Pancreatic enzymes</u> Dulaglutide is associated with mean increases from baseline in pancreatic enzymes (lipase and/or pancreatic amylase) of 11 % to 21 % (see section 4.4). In the absence of other signs

Class	Product	Section 4.4 Warnings and Precautions	Section 4.8 Adverse Reactions
			and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.
GLP-1	Bydureon (exenatide)	Acute pancreatitis Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis. There have been spontaneously reported events of acute pancreatitis with prolonged-release exenatide. Resolution of pancreatitis has been observed with supportive treatment, but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, prolonged-release exenatide should be discontinued; if acute pancreatitis is confirmed, prolonged-release exenatide should not be restarted. Caution should be exercised in patients with a history of pancreatitis.	Since immediate-release exenatide has been marketed, acute pancreatitis has been reported with a frequency not known and acute renal failure has been reported uncommonly (see section 4.4). Acute pancreatitis is listed with a frequency of 'Not known' with a cross reference to 4.4.
GLP-1	Saxenda (liraglutide)	Pancreatitis Use of GLP-1 receptor agonists has been associated with the risk of developing acute pancreatitis. There have been few reported events of acute pancreatitis with liraglutide. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, liraglutide should be discontinued; if acute pancreatitis is confirmed, liraglutide should not be restarted. Caution should be exercised in patients with a history of pancreatitis.	Pancreatitis is listed with a frequency of 'Unknown', with a cross reference to 4.4.
GLP-1	Victoza (liraglutide)	Acute Pancreatitis Text same as Saxenda.	Pancreatitis (including necrotising pancreatitis) is listed with a frequency of 'Very rare'.

Class	Product	Section 4.4 Warnings and Precautions	Section 4.8 Adverse Reactions
			Pancreatitis Few cases (<0.2%) of acute pancreatitis have been reported during long-term clinical trials with Victoza. Pancreatitis was also reported post-marketing.
GLP-1	Lyxumia (lixisenatide)	Acute pancreatitis Use of glucagon-like peptide-1 (GLP-1) receptor agonists has been associated with a risk of developing acute pancreatitis. There have been few reported events of acute pancreatitis with lixisenatide although a causal relationship has not been established. Patients should be informed of the characteristic symptoms of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, lixisenatide should be discontinued ; if acute pancreatitis is confirmed, lixisenatide should not be restarted. Caution should be exercised in patients with a history of pancreatitis.	
TZDs	pioglitazone	N/A	N/A
TZDs	rosiglitazone (withdrawn)		
TZDs	troglitazone (withdrawn)		
Sulfonylureas	glipizide	N/A	N/A
Sulfonylureas	glibenclamide /glyburide	N/A	N/A
Sulfonylureas	glimepiride	N/A	N/A
Sulfonylureas	chlorpropamide (not approved in EU)		
Sulfonylureas	tolazamide (not approved in EU)		
Sulfonylureas	tolbutamide	N/A	N/A
Sulfonylureas	acetohexamide (not approved in EU)		
Insulin	insulin	N/A	N/A
Other AHAs	acarbose	N/A	N/A
Other AHAs	bromocriptine	N/A	N/A
Other AHAs	miglitol	N/A	N/A
Other AHAs	nateglinide	N/A	N/A
Other AHAs	repaglinide	N/A	N/A

Class	Product	Section 4.4 Warnings and Precautions	Section 4.8 Adverse Reactions
Metformin	metformin	N/A	N/A
SGLT2 inhibitors	canagliflozin	N/A	N/A
SGLT2 inhibitors	dapagliflozin propanediol monohydrate	N/A	N/A
SGLT2 inhibitors	empagliflozin	N/A	N/A

ANNEX 2.

Table below presents the 24 negative controls that will be used to perform empirical calibration of the study estimates and to generate calibrated p-values.

Concept Identifier	Concept Name
444100	Mood disorder
443617	Conduct disorder
442077	Anxiety disorder
441589	Endocarditis
440374	Obsessive-compulsive disorder
438688	Sarcoidosis
435783	Schizophrenia
434008	White blood cell disorder
432876	Bipolar I disorder
432251	Disease caused by parasite
378752	Corneal opacity
378161	Disorder of ear
376382	Tension-type headache
320136	Disorder of respiratory system
319843	Mitral valve disorder
314054	Aortic valve disorder
257012	Chronic sinusitis
257007	Allergic rhinitis
255891	Lupus erythematosus
193016	Cystic disease of kidney
139057	Disorder of oral soft tissues
138225	Disorder of sebaceous gland
134681	Diffuse spasm of esophagus
31057	Disorder of pharynx

These baseline mock tables may serve as an example and actual presentation (eg, format) may be different.

If produced, it should be generated for each pairwise comparison and for each database

Table XX. Baseline Characteristics before and after Propensity-Score Matching by New User Treatment Cohort

	Before Matching			After Matching		
Baseline Characteristics	**[Comparator] n (%)**	**Cana n (%)**	**Standardized Difference**	**[Comparator] n (%)**	**Cana n (%)**	**Standardized Difference**
Total, N=						
Age, years						
Mean (SD)						
Median						
Age Categories (vary across databases)						
18-44						
45-54						
55-64						
65-74						
75-84						
85+						
Gender						
Male						
Female						
Baseline AHA use						
Metformin (any)						
Metformin plus ≥ 1 AHA						
DPP-4						
GLP-1						
TZDs						
Sulfonylureas						
Insulin						
Other AHA						
Average duration of follow-up (PP and ITT respectively), years						
Mean (SD)						
Median						
Comorbidities of Interest						
Congestive heart failure						
Cardiomyopathy						
Acute coronary syndrome						
COPD						
Dementia						
Hemiplegia/Paraplagia						
Mild liver disease						
Moderate/severe liver disease						
HIV						
Hyperlipidemia						
Hypertension						

Table XX. Baseline Characteristics before and after Propensity-Score Matching by New User Treatment Cohort

	Before Matching			After Matching		
Baseline Characteristics	**[Comparator] n (%)**	**Cana n (%)**	**Standardized Difference**	**[Comparator] n (%)**	**Cana n (%)**	**Standardized Difference**
Stroke						
TIA						
Malignancy						
Metastatic solid tumor						
Myocardial Infarction						
Peptic ulcer disease						
Peripheral vascular disease						
Renal disease						
End-stage renal disease						
Rheumatic disease						
Venous thromboembolism						
Biliary disease						
Pancreatic disease						
Acute pancreatitis						
Chronic pancreatitis						
Other pancreatic disease						
Alcoholism						
Obesity						
CCI Score						
Mean (SD)						
Number of AHA baseline medications						
Mean (SD)						
Median						
Index date						
year						
Baseline medication						
ACEi						
ARBs						
Antiarrhythmics						
Beta-blockers						
Calcium channel blockers						
Digoxin						
Diuretics						
Statins						
H2 Antagonists						
Proton pump inhibitors						
NSAIDS						
SSRI antidepressants						

Note: These baseline mock tables may serve as an example and actual presentation may change. If produced, it should be generated for each pairwise comparison and for each database

Table xx: Acute Pancreatitis Crude Incidence Rate Summary among New Users of AHA therapies in [insert: database name]: Non-Matched Cohorts

Please note that tables/figures are mocked up as examples, and not all changes made to the protocol are reflected in those mock-up tables/figures. The actual format of the presentation of the results could differ from the mock-ups as well.

Note: this table will be generated for the following sets of analysis for each claims database:

1) ITT approach: non-matched cohorts
2) PP (on-treatment) approach: non-matched cohorts

Cohort	Number of exposed persons	Person-years at risk	Persons with acute pancreatitis post- exposure	Incidence rate (per 1,000 person-years)	
Canagliflozin					
DPP-4 new users					
Alogliptin					
…					
GLP-1 new users					
Albiglutide					
…					
TZD new users					
Pioglitazone					
…					
Sulfonylureas new users					
Glipizide					
…					
Insulin new users					
Other AHA new users					
Acarbose					
...					
SGLT2i new users					
Dapagliflozin					
Empagliflozin					

Table xx: Acute Pancreatitis Crude Incidence Rate Summary among New Users of AHA Therapies in [insert: database name]: Propensity-Score Matched Cohorts

Note: The table below will be generated for each database using ITT and PP approaches

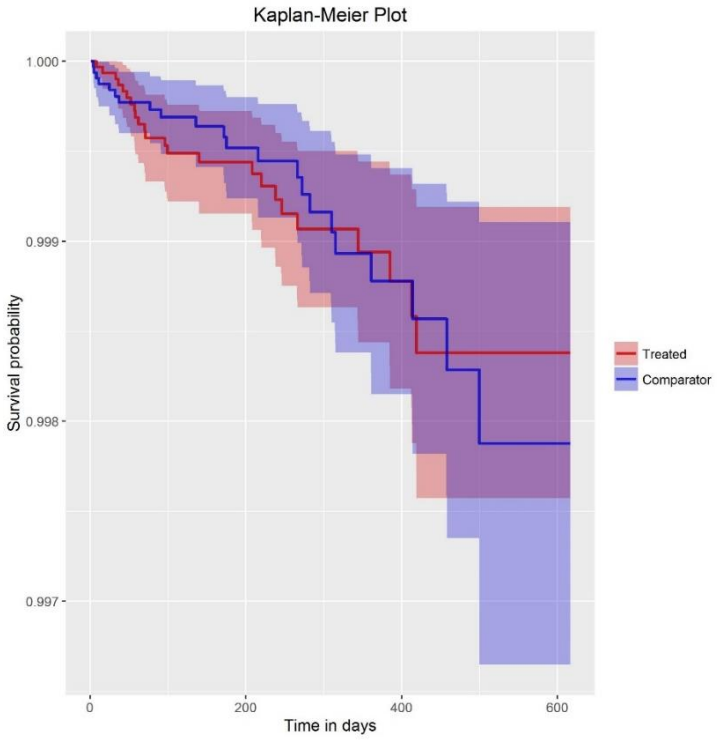
1) ITT approach: propensity-score matched cohorts
2) PP (on-treatment) approach: propensity-score matched cohorts

	Pairwise Comparison Cohorts	Number of exposed persons	Person-years at risk	Persons with acute pancreatitis post- exposure	Incidence rate (per 1,000 person-years)	
1	Canagliflozin					
	DPP-4					
2	Canagliflozin					
	GLP-1					
3	Canagliflozin					
	TZDs					
4	Canagliflozin					
	sulfonylureas					
5	Canagliflozin					
	Insulin					
6	Canagliflozin					
	Other AHAs					
Versus DPP-4 AHA						
7	Canagliflozin					
	Alogliptin					
	…					
Versus GLP-1 AHA						
12	Canagliflozin					
	Albiglutide					
	…					
Versus TZD AHA						
17	Canagliflozin					
	Pioglitazone					
	…					
Versus Sulfonylureas						
20	Canagliflozin					
	Glipizide					
	…					
Versus Other AHAs						
27	Canagliflozin					
	Acarbose					
	...					
Versus SGLT2i						
32	Canagliflozin					
	Dapagliflozin					
33	Canagliflozin					
	Empagliflozin					

Figure XX: Kaplan-Meier of time-to-event attrition in comparative analysis matched cohorts

Note: this figure will be generated for 33 pairwise comparisons for each database:

1) ITT approach: propensity-score matched pairwise comparison
2) PP approach: propensity-score matched pairwise comparison



Note this table will be generated for each database using both the ITT and PP approaches, respectively

Note: The results in this table (eg, the effect sizes and 95% CIs) could be presented as forest plot(s)

Table XX. Treatment Comparison of Acute Pancreatitis for Canagliflozin New Users versus Comparator AHA New Users [database]

	Comparison of event rate per 100 person-years (matched cohorts)							
	Comparator AHA		Canagliflozin		Hazard ratio (non-calibrated)		(calibrated)	Multiplicity-adjusted
Outcomes: acute pancreatitis	# of events	Rate	# of events	Rate	(95% CI)	p-value	p-value	p-value
ITT approach								
Canagliflozin vs. Metformin	xxx	x.x	xxx	x.x	x.x (x.x, x.x)	x.xxx		x.xxx
DPP-4 new users								
Canagliflozin vs. Alogliptin	xxx	x.x	xxx	x.x	x.x (x.x, x.x)	x.xxx		x.xxx
…	xxx	x.x	xxx	x.x	x.x (x.x, x.x)	x.xxx		x.xxx
GLP-1 new users								
Canagliflozin vs. Albiglutide	xxx	x.x	xxx	x.x	x.x (x.x, x.x)	x.xxx		x.xxx
…	xxx	x.x	xxx	x.x	x.x (x.x, x.x)	x.xxx		x.xxx
TZD new users								
Canagliflozin vs. Pioglitazone	xxx	x.x	xxx	x.x	x.x (x.x, x.x)	x.xxx		x.xxx
…	xxx	x.x	xxx	x.x	x.x (x.x, x.x)	x.xxx		x.xxx
Sulfonylureas new users								
Canagliflozin vs. Glipizide	xxx	x.x	xxx	x.x	x.x (x.x, x.x)	x.xxx		x.xxx
…	xxx	x.x	xxx	x.x	x.x (x.x, x.x)	x.xxx		x.xxx
Insulin new users								
Canagliflozin vs. Insulin	xxx	x.x	xxx	x.x	x.x (x.x, x.x)	x.xxx		x.xxx
Other AHA new users								
Canagliflozin vs. Acarbose	xxx	x.x	xxx	x.x	x.x (x.x, x.x)	x.xxx		x.xxx
...	xxx	x.x	xxx	x.x	x.x (x.x, x.x)	x.xxx		x.xxx
SGLT2i new users								
Canagliflozin vs. Dapagliflozin	xxx	x.x	xxx	x.x	x.x (x.x, x.x)	x.xxx		x.xxx
Canagliflozin vs. Empagliflozin	xxx	x.x	xxx	x.x	x.x (x.x, x.x)	x.xxx		x.xxx

T2DM definition:

People having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of Secondary Diabetes[8] occurring between all days Before and 0 days After index
- and at least 1 occurrences of a condition occurrence of Type II Diabetes[12] occurring between all days Before and 0 days After index
- and exactly 0 occurrences of a condition occurrence of Type I Diabetes[11] occurring between all days Before and 0 days After index

Codes for Secondary, Type I, and Type II diabetes.

8. Secondary Diabetes

Here is the list of ICD9 codes included in the Secondary Diabetes concept list:

Id	Code	Name
44836911	249.0	Secondary diabetes mellitus, without mention of complication
44832187	249	Secondary diabetes mellitus
44820680	249.00	Secondary diabetes mellitus without mention of complication, not stated as uncontrolled, or unspecified
44832188	249.01	Secondary diabetes mellitus without mention of complication, uncontrolled
44835748	249.10	Secondary diabetes mellitus with ketoacidosis, not stated as uncontrolled, or unspecified
44835747	249.1	Secondary diabetes mellitus with ketoacidosis
44820681	249.11	Secondary diabetes mellitus with ketoacidosis, uncontrolled
44831044	249.2	Secondary diabetes mellitus with hyperosmolarity
44819498	249.20	Secondary diabetes mellitus with hyperosmolarity, not stated as uncontrolled, or unspecified
44819499	249.21	Secondary diabetes mellitus with hyperosmolarity, uncontrolled
44835749	249.30	Secondary diabetes mellitus with other coma, not stated as uncontrolled, or unspecified
44832189	249.3	Secondary diabetes mellitus with other coma
44836912	249.31	Secondary diabetes mellitus with other coma, uncontrolled
44834547	249.4	Secondary diabetes mellitus with renal manifestations
44833364	249.40	Secondary diabetes mellitus with renal manifestations, not stated as uncontrolled, or unspecified
44835750	249.41	Secondary diabetes mellitus with renal manifestations, uncontrolled
44828788	249.5	Secondary diabetes mellitus with ophthalmic manifestations
44822932	249.50	Secondary diabetes mellitus with ophthalmic manifestations, not stated as uncontrolled, or unspecified
44836913	249.51	Secondary diabetes mellitus with ophthalmic manifestations, uncontrolled
44829876	249.60	Secondary diabetes mellitus with neurological manifestations, not stated as uncontrolled, or unspecified

Id	Code	Name
44825262	249.6	Secondary diabetes mellitus with neurological manifestations
44822933	249.61	Secondary diabetes mellitus with neurological manifestations, uncontrolled
44828789	249.7	Secondary diabetes mellitus with peripheral circulatory disorders
44821785	249.70	Secondary diabetes mellitus with peripheral circulatory disorders, not stated as uncontrolled, or unspecified
44835751	249.71	Secondary diabetes mellitus with peripheral circulatory disorders, uncontrolled
44828790	249.80	Secondary diabetes mellitus with other specified manifestations, not stated as uncontrolled, or unspecified
44821786	249.8	Secondary diabetes mellitus with other specified manifestations
44825263	249.81	Secondary diabetes mellitus with other specified manifestations, uncontrolled
44828792	249.90	Secondary diabetes mellitus with unspecified complication, not stated as uncontrolled, or unspecified
44828791	249.9	Secondary diabetes mellitus with unspecified complication
44829877	249.91	Secondary diabetes mellitus with unspecified complication, uncontrolled

11. Type I Diabetes

Here is the list of ICD9 codes included in the Type I Diabetes concept list:

Id	Code	Name
44820682	250.01	Diabetes mellitus without mention of complication, type I [juvenile type], not stated as uncontrolled
44821787	250.03	Diabetes mellitus without mention of complication, type I [juvenile type], uncontrolled
44824071	250.11	Diabetes with ketoacidosis, type I [juvenile type], not stated as uncontrolled
44822934	250.13	Diabetes with ketoacidosis, type I [juvenile type], uncontrolled
44832190	250.21	Diabetes with hyperosmolarity, type I [juvenile type], not stated as uncontrolled
44832191	250.23	Diabetes with hyperosmolarity, type I [juvenile type], uncontrolled
	250.31	Diabetes with other coma, type I [juvenile type], not stated as uncontrolled
44820683	250.33	Diabetes with other coma, type I [juvenile type], uncontrolled
44822935	250.41	Diabetes with renal manifestations, type I [juvenile type], not stated as uncontrolled
44834549	250.43	Diabetes with renal manifestations, type I [juvenile type], uncontrolled
44822936	250.51	Diabetes with ophthalmic manifestations, type I [juvenile type], not stated as uncontrolled
44820684	250.53	Diabetes with ophthalmic manifestations, type I [juvenile type], uncontrolled
44831046	250.61	Diabetes with neurological manifestations, type I [juvenile type], not stated as uncontrolled
44819501	250.63	Diabetes with neurological manifestations, type I [juvenile type], uncontrolled
44825264	250.71	Diabetes with peripheral circulatory disorders, type I [juvenile type], not stated as uncontrolled

Id	Code	Name
44819502	250.73	Diabetes with peripheral circulatory disorders, type I [juvenile type], uncontrolled
44836918	250.81	Diabetes with other specified manifestations, type I [juvenile type], not stated as uncontrolled
44833368	250.83	Diabetes with other specified manifestations, type I [juvenile type], uncontrolled
44829881	250.91	Diabetes with unspecified complication, type I [juvenile type], not stated as uncontrolled
44819504	250.93	Diabetes with unspecified complication, type I [juvenile type], uncontrolled

12. Type II Diabetes

Here is the list of ICD9 codes included in the Type II Diabetes listing:

Id	Code	Name
44834547	249.4	Secondary diabetes mellitus with renal manifestations
44833364	249.40	Secondary diabetes mellitus with renal manifestations, not stated as uncontrolled, or unspecified
44835750	249.41	Secondary diabetes mellitus with renal manifestations, uncontrolled
44828788	249.5	Secondary diabetes mellitus with ophthalmic manifestations
44822932	249.50	Secondary diabetes mellitus with ophthalmic manifestations, not stated as uncontrolled, or unspecified
44836913	249.51	Secondary diabetes mellitus with ophthalmic manifestations, uncontrolled
44836914	250.00	Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled
44836915	250.02	Diabetes mellitus without mention of complication, type II or unspecified type, uncontrolled
44829878	250.10	Diabetes with ketoacidosis, type II or unspecified type, not stated as uncontrolled
44824072	250.12	Diabetes with ketoacidosis, type II or unspecified type, uncontrolled
44836916	250.20	Diabetes with hyperosmolarity, type II or unspecified type, not stated as uncontrolled
44826459	250.2	Diabetes mellitus with hyperosmolarity
44824073	250.22	Diabetes with hyperosmolarity, type II or unspecified type, uncontrolled
44836917	250.3	Diabetes with other coma
44826460	250.30	Diabetes with other coma, type II or unspecified type, not stated as uncontrolled
44832193	250.32	Diabetes with other coma, type II or unspecified type, uncontrolled
44831045	250.40	Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled
44824074	250.4	Diabetes with renal manifestations
44832194	250.42	Diabetes with renal manifestations, type II or unspecified type, uncontrolled
44828794	250.5	Diabetes with ophthalmic manifestations
44819500	250.50	Diabetes with ophthalmic manifestations, type II or unspecified type, not stated as uncontrolled

Id	Code	Name
44829879	250.52	Diabetes with ophthalmic manifestations, type II or unspecified type, uncontrolled
44828795	250.60	Diabetes with neurological manifestations, type II or unspecified type, not stated as uncontrolled
44833366	250.62	Diabetes with neurological manifestations, type II or unspecified type, uncontrolled
44827616	250.70	Diabetes with peripheral circulatory disorders, type II or unspecified type, not stated as uncontrolled
44833367	250.72	Diabetes with peripheral circulatory disorders, type II or unspecified type, uncontrolled
44831047	250.80	Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled
44826461	250.82	Diabetes with other specified manifestations, type II or unspecified type, uncontrolled
44827617	250.90	Diabetes with unspecified complication, type II or unspecified type, not stated as uncontrolled
44829882	250.92	Diabetes with unspecified complication, type II or unspecified type, uncontrolled
44826573	362.0	Diabetic retinopathy
44831148	362.01	Background diabetic retinopathy
44833465	362.02	Proliferative diabetic retinopathy
44823040	362.03	Nonproliferative diabetic retinopathy NOS
44834647	362.04	Mild nonproliferative diabetic retinopathy
44832299	362.05	Moderate nonproliferative diabetic retinopathy
44832300	362.06	Severe nonproliferative diabetic retinopathy
44821870	362.07	Diabetic macular edema
44832301	362.2	Other proliferative retinopathy
44833484	366.41	Diabetic cataract

ANNEX 3. LIST OF STAND-ALONE DOCUMENTS

Document number	Title
1	Enumeration of the protocol specified comparative analyses