Boehringer Ingelheim

Non-Interventional Study (NIS) Protocol

Document Number:	c37704615-01
BI Study Number:	1245-0201
BI Investigational Product(s):	Jardiance® (empagliflozin)
Title:	Post-authorization safety study (PASS) to assess the risk of acute pancreatitis in type 2 diabetes mellitus (T2DM) patients newly initiating empagliflozin compared to other oral non-incretin/non-sodium glucose co-transporter-2 inhibitors (SGLT2)-containing glucose lowering drugs
Brief lay title:	To assess the risk of acute pancreatitis in patients with type 2 diabetes mellitus treated with empagliflozin
Protocol version identifier:	1.0
Date of last version of protocol:	NA
PASS:	Yes
EU PAS register number:	EUPAS44267
Active substance:	A10BK03 Empagliflozin
Medicinal product:	Jardiance®
Product reference:	NA
Procedure number:	NA
Marketing authorization holder(s):	[redacted]

Joint PASS:	No
Research question and objectives:	The main objective of the study is to compare the risk of acute pancreatitis in patients with type 2 diabetes mellitus (T2DM) newly initiating empagliflozin to that of patients newly initiating other oral non-incretin/non-sodium glucose co-transporter-2 inhibitors (SGLT2i)-based glucose lowering drugs.
Country(-ies) of study:	United States of America (USA)
Author:	[redacted] Global Epidemiology, Boehringer Ingelheim International GmbH [redacted] Global Epidemiology, Boehringer Ingelheim International GmbH [redacted]
In case of PASS, add: **MAH contact person:**	[redacted]
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Date:	10 December 2021

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2. LIST OF ABBREVIATIONS

BI	Boehringer Ingelheim
CI	Confidence Interval
CPRD	Clinical Practice Research Databases
CPT	Current Procedural Terminology codes
CTS-PS	Calendar-time specific (CTS) propensity scores (PS)
DPP-4i	Dipeptidyl peptidase 4 inhibitors
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
HbA1c	Hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act of 1996
HR	Hazard Ratio
HCRU	Healthcare resource utilization
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ISPE	International Society for Pharmacoepidemiology
LOINC	Logical Observation Identifiers Names and Codes
NIS	Non interventional study
NPV	Negative Predictive Value
NSAIDs	Non-steroidal anti-inflammatory drugs
Optum CDM	Optum Clinformatics® Data Mart
PASS	Post-authorization safety study
PPV	Positive Predictive Value
PS	Propensity scores
PSUR	Periodic Safety Update Report
PY	Person-Year
RMP	Risk Management Plan
SEAP	Statistical Epidemiological Analysis Plan

SGLT2i	Sodium glucose co-transporter-2 inhibitor
SU	Sulfonylurea
T2DM	Type 2 diabetes mellitus
Truven Marketscan CCAE	Truven Marketscan Commercial Claims and Encounters
Truven Marketscan MDCR	Truven Marketscan Medicare Supplemental (MDCR)
TZD	Thiazolidinediones
UK	United Kingdom
US	United States

3. RESPONSIBLE PARTIES

Principal Investigators of the Protocol:

Boehringer Ingelheim:
- [redacted] as of January 2020
- [redacted] until September 2021
- [redacted] until April 2020
- [redacted] as of January 2021

[redacted]

4. ABSTRACT

Name of company:			
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Name of finished medicinal product: Jardiance®			
Name of active ingredient: A10BK03 Empagliflozin			
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Title of study:	Post-authorization safety study (PASS) to assess the risk of acute pancreatitis in type 2 diabetes mellitus (T2DM) patients newly initiating empagliflozin compared to other oral non-incretin/non-sodium glucose co-transporter-2 inhibitors (SGLT2)-containing glucose lowering drugs		
Rationale and background:	Empagliflozin is a sodium glucose co-transporter-2 inhibitor (SGLT2i) which promotes renal excretion of glucose and lowers elevated blood glucose levels in patients with T2DM [P14-09057]. Pancreatitis is defined as an important potential risk in the risk management plan (RMP) for empagliflozin. This post-authorization safety study (PASS) is voluntarily performed to assess the risk of acute pancreatitis in patients with T2DM newly initiating empagliflozin compared to the initiators of other oral non-incretin/non-SGLT2i–based glucose lowering drugs. Studies have shown that the risk of acute pancreatitis is higher in patients with T2DM and established cardiovascular disease (eCVD) than those without these disorders [R10-6620, R10-2088, R21-0209]. In the past ten years, numerous studies assessed the association between pancreatitis and glucose lowering drugs in the United States (US) [R18-1760, P19-09574, R13-3873, R11-0776, R19-3424, P13-04390, P13-16900, R20-0777], Canada [P19-09574], United Kingdom (UK) [P17-03843, P14-06737], Denmark [P15-05208], and in Asia [R19-3425, R19-3426, R19-3427, R19-3428, R19-3429, R11-5180, P16-11950, R19-3430]. Certain diabetes drug classes, for instance incretin-containing medications including dipeptidyl peptidase 4 inhibitors (DPP-4i; such as sitagliptin, saxagliptin, linagliptin, alogliptin) and glucagon-like peptide-1 receptor agonists (GLP-1 RA; such as exenatide, liraglutide, lixisenatide, dulaglutide, semaglutide) [P13-15588]), have been associated with the risk of developing acute pancreatitis. Results vary from protective to null associations to a 2-3 fold elevated risk of acute pancreatitis depending on the design, population, treatments and comparators studied [R18-1760, P19-09574, R13-3873, R11-0776, R19-3424, P13-04390, P13-16900, R20-0777, P19-09574, P17-03843, P14-06737, P15-05208, R19-3425, R19-3426, R19-3427, R19-3428, R19-3429, R11-5180, P16-11950, R19-3430]. Recently an observational study was conducted using large claims databases in the US (Truven Marketscan Commercial Claims and Encounters (CCAE) and Medicare Supplemental (MDCR) Database, and Optum Extended Socio-Economic (SES)) to assess the risk of acute pancreatitis in T2DM patients newly exposed to		

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	canagliflozin compared to other oral glucose lowering drugs. Six different cohorts of new users of DPP-4is, GLP-1 RAs, sulfonylureas (SUs), thiazolidinediones (TZD), insulin, and other antihyperglycemic agents (AHA) were identified and compared separately with the new users of canagliflozin. Overall, no consistent difference in the risk of acute pancreatitis was observed when comparing canagliflozin with other oral glucose lowering drugs, not with regards to databases, nor with regards to different comparator groups [RRA-21430]. This inconsistent observation could have several reasons: 1) cohorts were not properly matched concerning previous use of AHA 2) cohorts were not matched with regards to acute pancreatitis risk factors e.g. gall stones 3) concomitant AHA treatment were allowed without restriction. Moreover, because of the heterogenous comparator and residual confounding, no conclusion could be made based on the study results. Considering methodological challenges discussed above, this voluntary PASS was designed to investigate the risk of acute pancreatitis in new users of empagliflozin compared to the new users of other oral non-incretin/non-SGLT2i-containing glucose lowering drugs. Comparison groups in this study are selected based on clinical guideline recommendations and current real-world patterns of use for oral glucose lowering drugs.		
Research question and objectives:	The objective of the study is to compare the incidence rate of acute pancreatitis in T2DM patients initiating empagliflozin to new users of other oral non-incretin/non-SGLT2i-containing glucose lowering drugs between 1 August 2014 and the latest data-cut available in Marketscan (30 September 2020) and Optum (31 March 2021).		
Study design:	Non interventional study (NIS) using existing data - new user active comparator cohort study		
Population:	Truven Marketscan Commercial Claims and Encounters (CCAE), Truven Marketscan Medicare Supplemental (MDCR), and Optum Clinformatics® Data Mart [CDM] databases will be used in this study. All adults with a recorded diagnosis of T2DM who initiated empagliflozin or other oral non-incretin/non-SGLT2i-containing glucose lowering drugs (metformin, SU, or TZD) between 1 August 2014 and the latest data-cut available in Marketscan (30 September 2020) and Optum (31 March 2021. Comparison groups are selected based on clinical guideline recommendations and current real-world patterns of use for oral glucose lowering drugs in patients with T2DM. First-line therapy in the US and most countries according to the guidelines is metformin. SUs, TZDs, and incretin therapies are next non-SGLT2i alternatives		

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for the treatment of T2DM, except for insulin. Several studies have reported associations between the use of incretin-based medications (including DPP-4is and GLP-1 RAs) and the risk of developing acute pancreatitis [P13-15588]. Hence, DPP-4is and GLP-1 RAs are excluded as comparators for this study.

Diabetes is a risk factor for acute pancreatitis [R10-6620, R10-2088], but there is limited information on the duration and severity of diabetes in the US claims databases. Creating comparison groups based on treatment line might be helpful to decrease residual confounding. Therefore, to assess the risk of acute pancreatitis we decided to conduct head-to-head comparative analyses (pending feasibility assessment and adequate sample size) using the separate therapy lines outlined below [P17-01404]:

- Monotherapy: Empagliflozin vs. metformin
- Dual therapy: Empagliflozin vs. SU (both on a background of metformin)
- Triple therapy: Empagliflozin vs. TZD (both on a background of metformin plus SU)

Separate analysis of the two databases within each treatment line is the ideal approach. However, if there are not enough study participants in the Optum and MarketScan databases in each therapy line, a meta-analysis of each therapy line will be conducted between Optum and MarketScan (pending heterogeneity and sample size assessments).

Other combinations of empagliflozin (e.g. empagliflozin on a background of SU or TZD, or empagliflozin on a background of SU and TZD) will not be assessed in this study due to the small sample size [Feasibility assessment report November 2021, data on file].

Overall inclusion and exclusion criteria are listed below.÷

General inclusion criteria: Patients must meet all of the following criteria to be eligible for inclusion in the study:

- Patients >= 18 years old
- A diagnosis of T2DM as demonstrated by at least one qualifying diagnosis code (International Classification of Diseases (ICD)-9-CM diagnosis code of 250.x0 or 250.x2; ICD-10-CM diagnosis code of E11.x) from any encounter type recorded in the claims in the 6 months prior to the drug initiation.
- Have at least 6 months of continuous registration in the database prior to initiation of empagliflozin or a comparator drug

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	Exclusion criteria: Patients meeting any of the following criteria will be excluded from the study: • Patients with missing or ambiguous age or sex information. • Use of a SGLT2i, DPP-4i or GLP-1 RA in the 6 months prior to study drug initiation. • Chronic use of insulin in the outpatient setting in the 6 months prior to the study drug initiation. This criterion will help to remove severe cases of diabetes and reduce the risk of residual confounding as diabetes is a risk factor for developing acute pancreatitis [R10-6620, R10-2088]. • Patients with type 1 diabetes mellitus (T1DM) defined as at least 1 inpatient or outpatient ICD-9-CM diagnosis code of 250.x1 or 250.x3 or ICD-10-CM diagnosis code of E10.x in the 6 months prior to the study drug initiation. • Patients with secondary diabetes or gestational diabetes in the 6 months prior to the study drug initiation (codes are listed in Appendix 3). • Claims for acute or chronic pancreatitis, pancreatic cancer, or other disease of the pancreas any time prior to the study drug initiation. Treatment line specific inclusion criteria (if feasibility assessment would allow an adequately/sufficiently powered analysis) are: • For the monotherapy cohort, patients should be new users of empagliflozin or metformin (comparator). To quantify as a new user, no use of either of the two drugs (empagliflozin or metformin) in the previous 6 months is permitted. • For the dual therapy cohort, patients should be new users of empagliflozin (on a background of metformin) or new users of SU on a background of metformin (comparator). To quantify as a new user, no use of either of the two drugs (empagliflozin or SUs) in the previous 6 months is permitted. • For the triple therapy cohort, patients should be new users of empagliflozin (on a background of metformin and SU) or new users of TZD on a background of metformin and SU (comparator). To quantify as a new user, no use of either of the 2 drugs (empagliflozin or TZDs) in the previous 6 months is permitted.		
Variables:	Exposure variables will include: • New therapy with empagliflozin for the treatment of T2DM (index medication		

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is empagliflozin)

- As monotherapy
- On a background of metformin
- On a background of metformin and SU

- New therapy with a non-incretin/non-SGLT2i-containing oral hypoglycaemic agent for the treatment of T2DM
  - Metformin monotherapy: index medication is metformin
  - SU (on a background of metformin): index medication is SU
  - TZD (on a background of metformin and SU): index medication is TZD

Fixed-dose combinations will be considered equivalent to free combination regimens, e.g. Synjardy will be considered as dual therapy of empagliflozin on a background of metformin. Fixed dose combinations will be considered separately to describe switching, addition or stop, and for censoring patients.

Outcome: Primary outcome of this study is acute pancreatitis.

The following algorithm will be used to identify cases of acute pancreatitis [R20-3555, R20-3554]:

The presence of an acute pancreatitis diagnosis (ICD-9-CM 577.0 or ICD-10-CM K85) from any of the inpatient (not restricted to the primary diagnosis), outpatient, or emergency contacts diagnoses

AND

- A lipase measure within +/- 7 days of the acute pancreatitis diagnosis (using Logical Observation Identifiers Names and Codes (LOINC) of 3040-3 and 2572-6 or Current Procedural Terminology (CPT) code of 83690 for lipase)

AND

- An abdominal ultrasound within +/- 7 days of the acute pancreatitis diagnosis (using CPT codes of 76700 or 76705)

Covariates:

Several baseline patient characteristics will be captured in the 6 months prior to the index date. Some of these covariates will be included as covariates in the propensity scores (PS) model.

- Demographics
- Comorbidity indexes: Elixhauser comorbidity index [R14-4775], Charlson

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	comorbidity index • Diabetes specific complications • Comorbidities • Prior/concomitant use of other oral glucose lowering drugs • Prior/concomitant use of drug(s) associated with acute pancreatitis: - α-methyldopa, azodisalicylate, bezafibrate, cannabis, carbimazole, codeine, cytosine, arabinoside, dapsone, enalapril, furosemide, isoniazid, mesalamine, metronidazole, pentamidine, pravastatin, procainamide, pyritonol, simvastatin, stibogluconate, sulfamethoxazole, sulinda, tetracycline, valproic acid, all trans-retinoic acid, amiodarone, azathioprine, clomiphene, dexamethasone, ifosfamide, lamivudine, losartan, lynesterol/methoxyethinylestradiol, Mercaptopurine, meglumine, methimazole, nelfinavir, norethindronate/mestranol, omeprazole, premarin, sulfamethazole, trimethoprimsulfamethazole, acetaminophen, chlorthiazide, clozapine, didanosine, erythromycin, estrogen, L-asparaginase, pegasparagase, propofol, tamoxifen, azathioprine, sulfonamides, tetracyclines, alpha-methyldopa • Prior/concomitant use of other medications (e.g. cardiovascular medications etc.) • Other acute pancreatitis risk factors e.g. abdominal surgery, alcoholism and alcohol abuse, cystic fibrosis, gallstones and other gallbladder and biliary tract disorders, hyperparathyroidism, infection, injury to the abdomen, and lupus • Specific lab test results (when available)
Data sources:	Following claims databases in the US will be used in this study: • Truven Marketscan (CCAE and MDCR) Database • Optum Clinformatics® Data Mart [CDM]
Study size:	All patients with T2DM who newly initiate therapy with empagliflozin or study comparator and who meet the inclusion and exclusion criteria will be included in the analysis. Event rate of acute pancreatitis reported in patients with T2DM who are treated with canagliflozin was reported to be 2.2 per 1000 person-years (PY) [RRA-21430]. This rate was used for sample size calculation using the formula of Farrington and Manning (maximum likelihood method) [R14-3295].

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Null hypothesis H0: $\pi_2 / \pi_1 \geq 1.5$ (non-inferiority)

A single stage (fixed sample size) design was chosen.

For specified $\alpha = 0.05$ and rates $\pi_1 = 0.0022$ and $\pi_2 = 0$

.0022 (odds ratio of 1.000) the power (1 - β) is 80.0% if the test stages consist of the sample sizes given in the last two columns of the table.

The computation assumes an allocation ratio (n2/n1) = 1. It is assumed that all patients have 1 year of follow up.

Hazard ratio (HR)	**sign. level one-sided**	**α spent**	**β spent**	**power achieved**	**Observations per exposure group**	**Overall observations**
1.5	0.0500	0.0500	-	0.8000	34585.4	69170.8

ADDPLAN Adaptive Design Software 2019 and SAS 9.4 software ([redacted], [redacted]) were used to calculate the sample size.

Analysis of this study will be initiated as soon as a sufficient sample size to exclude a HR of 1.5 with 80% power is reached. Based on a feasibility assessment conducted in Optum and MarketScan databases using data between 1 August 2014 and the latest data-cut available in MarketScan (30 September 2020) and Optum (31 March 2021), the dual-therapy cohort was reported with the highest number of empagliflozin initiators, therefore a meta-analysis of the dual therapy cohorts including the data from the MarketScan and Optum databases will be the main analysis of this study as it will be the only powered analysis.

Data analysis:

The index date in this study is defined as the date of the first recorded claim for a qualifying prescription as a new user. Patients are required to have at least 6 months of continuous registration in the database prior to initiation of empagliflozin or a comparator drug (the look-back period). The look-back period includes the index date. The main analyses of this study will utilize a modified As-Treated (AT) approach.

Follow-up starts from the day after the index date until the first qualifying event has been met:

- The earliest claim for acute pancreatitis
- Addition of or switch to an incretin-based therapy (DPP-4is or GLP-1 RA) or insulin
- Addition of or switch to the within treatment line comparator index drug (see section 9.7)

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- Addition of or switch to an SGLT2i (in empagliflozin users, this would mean switch to a non-empagliflozin SGLT2i) (see section 9.7)
- Discontinuation of index drug
- End of study (date of death, date of end of registration in the database, or study end date).

As a first step, a propensity score (PS) will be estimated for each cohort member at the index date, based on the values of the observed covariates during the look-back period. In this study, propensity scores will be estimated by conducting multivariable logistic regression modelling and incorporating measured potential predictors of therapy as independent variables and exposure group status (empagliflozin group vs. comparator) as the outcome. We will use PS matching to balance a number of covariates. Key advantages of PS matching are that large numbers of covariates that can be adjusted for even when studying infrequent outcomes, the achieved covariate balance can be documented, multiple outcomes can be studied after a single matching process, [R13-1120] and patients who cannot find comparable pairs will be implicitly dropped out of the analysis increasing the validity of findings [R17-1404].

The propensity score will be used to match patients in a 1:1 ratio using a nearest-neighbor algorithm and calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score [R13-3590, R18-2599, R16-1227]. A 1:n variable ratio matching will not be used as it involves several complications while providing only a minimal gain in estimation precision [R17-1267]. If balance is not achieved, the PS model will be refitted using interaction terms [R18-2599]. PS balance achievement will be inspected by tabulating all patient characteristics by treatment status and by assessing the standardized differences. Any patient characteristics with a standardized difference of >10% will be considered for additional post-matching adjustment [R13-3590].

To account for patient characteristics changing over time, patients will be matched on the calendar quarter-year of initiation of the study medication. If we lose too many patients using this method, we may instead decide to match on year of initiation of index medication and then include calendar quarter-year variable in the PS model.

The incidence rates (per 1000 PY) and corresponding 95% confidence intervals (CI) of acute pancreatitis during the follow-up time will be calculated in each exposure group of interest in the unmatched and PS-matched cohorts.

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	Cox proportional hazards regression models based on time-to first acute pancreatitis event will be used to estimate hazard ratios (HR) and 95% CIs for each treatment line comparison of interest in the unmatched and PS-matched cohorts. Based on a feasibility assessment conducted in Optum and MarketScan databases using data between 1 August 2014 and the latest data-cut available in MarketSscan (30 September 2020) and Optum (31 March 2021), meta-analysis of the dual therapy cohorts including the data from the Marketscan MarketScan and Optum databases will be the main analysis of this study: • Dual therapy: Empagliflozin vs. SU (both on a background of metformin) All results will be presented for each database separately but if there is not enough sample size in each treatment line cohort in each database, after evaluating potential heterogeneity, meta-analysis techniques will be used to pool the treatment line cohorts of the 2 databases. Descriptive tables and all parameter estimates from the main and all sensitivity analyses will be pooled using meta-analytic methods assuming a fixed effects model, to avoid potential biases associated with random effects pooling in the context of few databases [R17-1410].		
Milestones:	The study period is between 1 August 2014 (start of data collection) and the latest data-cut available in Marketscan (30 September 2020) and Optum (31 March 2021) (end of data collection). In this multi database study, the start of data analysis will be in December 2021 and the final report will be available in Q3 2022.		

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	Not applicable
Start of data collection	1 August 2014
End of data collection	30 September 2020 for Marketscan and 31 March 2021 for Optum
<Registration in the EU PAS register>	29 November 2021
Start of data analysis	Q4 2021
End of data analysis	Q2 2022
Final report of study results:	Q3 2022

7. RATIONALE AND BACKGROUND

Empagliflozin is an oral hypoglycemic agent belonging to the sodium glucose co-transporter-2 inhibitor (SGLT2i) class, which promotes renal excretion of glucose and lowers elevated blood glucose levels in patients with type 2 diabetes mellitus (T2DM). Pancreatitis is defined as an important potential risk in the risk management plan (RMP) for empagliflozin. This post-authorization safety study (PASS) is voluntarily initiated by Boehringer Ingelheim (BI) to assess the risk of acute pancreatitis in patients with T2DM newly initiating empagliflozin compared to initiators of other oral non-incretin/non-SGLT2i-containing hypoglycemic agents.

Etiology and risk factors for pancreatitis

The most common etiologies for pancreatitis include cholelithiasis, alcohol use, and hypertriglyceridemia [P17-07372]. Other known causes of pancreatitis are trauma, surgery, cancer, anatomical variations of the pancreas and the pancreatic and biliary ducts, hypercalcemia, renal failure, and autoimmune disease [R20-0778]. Studies have shown that the risk of acute pancreatitis is higher in patients with T2DM and established cardiovascular disease (eCVD) than in patients without these disorders [R10-6620, R10-2088, R21-0209].

Different studies reported associations between the use of certain diabetes drug classes, for instance incretin-based medications (including dipeptidyl peptidase 4 inhibitors [DPP-4i; such as sitagliptin, saxagliptin, linagliptin, alogliptin] and glucagon-like peptide-1 receptor agonists [GLP-1 RA; such as exenatide, liraglutide, lixisenatide, dulaglutide, semaglutide] [P13-15588]) and the risk of developing acute pancreatitis.

Potential mechanisms of action for drugs known to cause acute pancreatitis include pancreatic duct constriction (e.g. opioids) or cytotoxic effects that are either direct or due to accumulation of a toxic metabolite or intermediary [P16-02537].

Pancreatitis reoccurs in up to 25% of patients following hospital admission for their first episode of acute pancreatitis, with smoking and/or alcohol abuse demonstrated as predominant risk factors [R20-0778].

Epidemiology of pancreatitis

The incidence of acute pancreatitis in T2DM patients varies, with rates from the Clinical Practice Research Databases (CPRD) in the United Kingdom (UK) ranging between 54 and 66 per 100,000 person-years (PY) and rates obtained from insurance claims databases in the United States (US) ranging between 422 and 560 per 100,000 PY [R10-5391, R10-6620, R10-2088]. The differences between these estimates may be due to the nature of the data sources and the populations studied.

In the past ten years, numerous studies assessed the association between pancreatitis and hypoglycemic agents in the US [R18-1760, P19-09574, R13-3873, R11-0776, R19-3424, P13-04390, P13-16900, R20-0777], Canada [P19-09574], UK [P17-03843, P14-06737], Denmark [P15-05208], and in Asia [R19-3425, R19-3426, R19-3427, R19-3428, R19-3429, R11-5180, P16-11950, R19-3430]. Certain diabetes drug classes, for instance incretin-containing medications (including dipeptidyl peptidase 4 inhibitors (DPP-4i; such as sitagliptin, saxagliptin, linagliptin, alogliptin) and glucagon-like peptide-1 receptor agonists (GLP-1 RA; such as exenatide, liraglutide, lixisenatide, dulaglutide, semaglutide) [P13-15588]), have been associated with the risk of developing acute pancreatitis. Results vary from protective to null associations to 2-3 fold elevated risk of acute pancreatitis depending on the design, population, treatments and comparators studied [R18-1760, P19-09574, R13-3873, R11-0776, R19-3424, P13-04390, P13-16900, R20-0777, P19-09574, P17-03843, P14-06737, P15-05208, R19-3425, R19-3426, R19-3427, R19-3428, R19-3429, R11-5180, P16-11950, R19-3430]. Recently an observational study was conducted using large claims databases in the US (Truven Marketscan Commercial Claims and Encounters (CCAE) and Medicare Supplemental (MDCR) Database, and Optum Extended Socio-Economic (SES)) to assess the risk of acute pancreatitis in T2DM patients newly exposed to canagliflozin compared to other oral hypoglycemic agents. Six different cohorts of new users of DPP-4is, GLP-1 RAs, sulfonylureas (SUs), thiazolidinediones (TZD), insulin, and other antihyperglycemic agents (AHA) were identified and compared separately with the new users of canagliflozin. Overall, no consistent difference in the risk of acute pancreatitis was observed when comparing canagliflozin with other oral glucose lowering drugs, not with regards to databases, nor with regards to different comparator groups [RRA-21430]. This inconsistent observation could have several reasons: 1) cohorts were not properly matched concerning previous use of AHA 2) cohorts were not matched with regards to acute pancreatitis risk factors e.g. gall stones 3) concomitant AHA treatment were allowed without restriction. Moreover, because of the heterogenous comparator and residual confounding, no conclusion could be made based on the study results.
Considering methodological challenges discussed above, this voluntarily PASS was designed to investigate the risk of acute pancreatitis in T2DM patients who initiated empagliflozin compared to new users of other oral non-incretin/non-SGLT2i-containing hypoglycemic agents between 1 August 2014 and the latest data-cut available in MarketScan (30 September 2020) and Optum (31 March 2021).

8. RESEARCH QUESTION AND OBJECTIVES

This non-interventional cohort study using data from two large US claims databases will assess the risk of acute pancreatitis among T2DM patients initiating empagliflozin between from 1 August 2014 to the latest data-cut available in MarketScan (30 September 2020) and Optum (31 March 2021).

Primary Objective:

To compare the risk of acute pancreatitis in patients with T2DM newly initiating empagliflozin to that of patients newly initiating other oral non-incretin/non-SGLT2i-containing hypoglycemic agents.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This study will use a new user cohort design comparing patients with T2DM who initiated empagliflozin to those who initiated other oral non-incretin/non-SGLT2i-containing glucose lowering drugs, based on electronically recorded longitudinal data from 2 large US claims databases.

9.2 SETTING

Data from 2 large US claims databases (MarketScan and Optum) will be used (from 1 August 2014 to the latest data-cut available in MarketScan (30 September 2020) and Optum (31 March 2021),). The study implements an active comparator new user design and compares patients who newly initiate empagliflozin to those who newly initiate other oral non-incretin/non-SGLT2i–containing glucose lowering drugs. Prior evidence suggested that incretin-based agents may be associated with an elevated risk of pancreatitis, therefore those agents will not be included in the analysis of this study.

9.2.1 Study sites

See section 9.4. for data sources.

9.2.2 Study population

All patients with a recorded diagnosis of T2DM who initiated empagliflozin or other oral non-incretin/non-SGLT2i-containing glucose lowering drugs (metformin, SU, or TZD) between 1 August 2014 and 31 October 2020 will be selected from the Truven MarketScan Commercial Claims and Encounters (CCAE), Truven MarketScan Medicare Supplemental (MDCR), and Optum Clinformatics® Data Mart [CDM] databases.

Comparison groups were selected based on clinical guideline recommendations and current real-world patterns of use for oral glucose lowering drugs. First-line therapy in the US and most countries according to the guidelines is metformin. SUs, TZDs, and incretin therapies are the primary non-SGLT2i alternatives for the treatment of T2DM. Several studies have reported associations between use of incretin-based medications (including dipeptidyl peptidase 4 inhibitors [DPP-4i; such as sitagliptin, saxagliptin, linagliptin, alogliptin] and glucagon-like peptide-1 receptor agonists [GLP-1 RA; such as exenatide, liraglutide, lixisenatide, dulaglutide, semaglutide] [P13-15588]) and risk of developing acute pancreatitis. Hence, DPP4is and GLP1RA are excluded from the comparators of this study.

Diabetes is a risk factor for acute pancreatitis [R10-6620, R10-2088], but there is limited information on the duration and severity of diabetes in the US claims databases. Creating comparison groups based on treatment line might be helpful to decrease residual confounding. Therefore, to assess the risk of acute pancreatitis we decided to conduct head-to-head comparative analyses (pending feasibility assessment and adequate sample size) using the stratified therapy lines outlined below [P17-01404]:

- Monotherapy: Empagliflozin vs. metformin —> index medication is empagliflozin or metformin
- Dual therapy: Empagliflozin vs. SU (both on a background of metformin) —> index medication is empagliflozin or SU
- Triple therapy: Empagliflozin vs. TZD (both on a background of metformin plus SU) —> index medication is empagliflozin or TZD

Separate analysis of the two databases within each treatment line is the ideal approach. However, if there are not enough study participants in the Optum and MarkeScan databases in each therapy line, a meta-analysis of each therapy line will be conducted between Optum and MarketScan (pending heterogeneity and sample size assessments).

Other combinations of empagliflozin (e.g. empagliflozin on a background of SU or TZD, or empagliflozin on a background of SU and TZD) will not be assessed in this study due to the small sample size [Feasibility assessment report November 2021, data on file].

From a feasibility assessment conducted in November 2021, it is known that there are not enough study participants in the Optum and MarketScan database in each therapy line and the dual-therapy cohort was reported with the highest number of empagliflozin initiators. Therefore, a meta-analysis of the dual therapy cohorts including the data from the MarketScan MarketScan and Optum databases will be the main analysis of this study.

Due to low sample size and inadequate power, analysis of the mono- and triple therapy cohorts cannot be assessed.

Overall inclusion and exclusion criteria are listed below:

Inclusion criteria: Patients must meet all of the following criteria to be eligible for inclusion in the study:

- Patients >= 18 years old
- A diagnosis of T2DM as demonstrated by at least one qualifying diagnosis code (International Classification of Diseases (ICD)-9-CM diagnosis code of 250.x0 or 250.x2; ICD-10-CM diagnosis code of E11.x) from any encounter type recorded in the claims in the 6 months prior to the drug initiation.
- Patients initiating empagliflozin (as monotherapy, on a background of metformin, or on a background of metformin and SU) or qualifying comparator (metformin monotherapy, SU on a background of metformin, or TZD on a background of metformin and SU) during the study period.

- Have at least 6 months of continuous registration in the database prior to initiation of empagliflozin or a comparator drug

Exclusion criteria: Patients meeting any of the following criteria will be excluded from the study:

- Patients with missing or ambiguous age or sex information.
- Use of a SGLT2i, DPP-4i or GLP-1 RA in the 6 months prior to study drug initiation.
- Chronic use of insulin in the outpatient setting in the 6 months prior to the study drug initiation (definition is added to the SEAP). This criterion will help us to remove severe cases of diabetes and reduce the risk of residual confounding as diabetes is a risk factor for developing acute pancreatitis [R10-6620, R10-2088].
- Patients with type 1 diabetes mellitus (T1DM) defined as at least 1 inpatient or outpatient International Classification of Diseases Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code of 250.x1 or 250.x3 or International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis code of E10.x in the 6 months prior to the study drug initiation.
- Patients with secondary diabetes or gestational diabetes in the 6 months prior to the study drug initiation.
- Claims for acute or chronic pancreatitis, pancreatic cancer, or other disease of the pancreas any time prior to the study drug initiation.

Treatment line specific inclusion criteria (if feasibility assessment would allow a powered analysis) are:

- For the monotherapy cohort, patients should be new users of empagliflozin or metformin (comparator). To quantify as a new user, no use of either of the two drugs (empaglifloin or metformin) in the previous 6 months is permitted.
- For the dual therapy cohort, patients should be new users of empagliflozin (on a background of metformin) or new users of SU on a background of metformin (comparator). To quantify as a new user, no use of either of the two drugs (empagliflozin or SUs) in the previous 6 months is permitted.
- For the triple therapy cohort, patients should be new users of empagliflozin (on a background of metformin and SU) or new users of TZD on a background of metformin and SU (comparator). To quantify as a new user, no use of either of the 2 drugs (empagliflozin or TZDs) in the previous 6 months is permitted.

All codes used in cohort creation are listed in Appendix 3 and 4.

9.2.3 Study visits

Not applicable.

9.2.4 Study discontinuation

Not applicable.

9.3 VARIABLES

The variables that will be used in this study are described below.

9.3.1 Exposures

For this study, eligible patients will be identified from prescriptions/dispensings for the following study medications of interest (index medications):

Study drug will include:
- New therapy with empagliflozin (index medication) for the treatment of T2DM:
    - As monotherapy
    - As dual therapy (on a background of metformin)
    - As triple therapy (on a background of metformin and SU)

Comparator will be:
- New therapy with an oral non-incretin/non-SGLT2i–containing hypoglycaemic agent for the treatment of T2DM:
    - As monotherapy (metformin monotherapy): index medication is metformin
    - As dual therapy (SU on a background of metformin): index medication is SU
    - As triple therapy (TZD on a background of metformin and SU): index medication is TZD

This leads to the following comparisons:

- Monotherapy: Empagliflozin vs metformin
- Dual therapy: Empagliflozin vs SU, both on background of metformin
- Triple therapy: Empagliflozin vs TZD, both on a background of metformin and SU

Fixed-dose combinations will be considered equivalent to their free combination regimens. For instance, initiators of Synjardy will be categorized as dual therapy of empagliflozin. Combinations beyond triple therapy (i.e., use of 4+ glucose lowering drugs) will not be considered.

The index date is defined as the date of the first recorded claim for a qualifying prescription as a new user. Patients are required to have at least 6 months of continuous registration in the database prior to initiation of empagliflozin or a comparator drug (the look-back period). The look-back period was specified to confirm new medication use (i.e., having a first prescription claim for empagliflozin or other oral non-incretin/non-SGLT2i-containing glucose lowering drugs without use in the prior 6 months) and describe baseline parameters, such as prior medical history and medications. The look-back period includes the index date.

The study will be conducted utilizing a modified “as-treated” approach. Study follow-up will start the day after initiation of index medication and will continue until:
- The first occurrence of the outcome

- The date of end of continuous registration in the database
- The date of death
- The date of study end (31 October 2020)
- The date of discontinuation of index medication (defined as the date of the last date of last dispensing + days supply + grace period). The grace period is a time period after exposure end during which observed outcomes are still attributed to the exposure. Grace period varies according to the specific outcome. In this study, for acute pancreatitis, we have 30 days [c18659315-02] grace period in the main analysis and 90 days in the sensitivity analysis [R18-1760, RRA-21430, P20-07536].
- The date of switch of index medication to another hypoglycaemic agent (see section 9.7.1. and SEAP)
- The date of addition of incretin-based therapy (with continuation of index therapy)
- The date of addition of SGLT2i (with continuation of index therapy)
- The date of addition of insulin (with continuation of index therapy)
- The date of addition of the within treatment line comparator index drug (with continuation of index therapy)

All definitions can be found in section 9.7.1. All codes used to define exposure variables are listed in Appendix 4.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

In this study we will use a modified version of an algorithm developed and validated in the [redacted] with a sensitivity of 89.8% and a specificity of 79.4% [R20-3555, R20-3554]. In the original algorithm, only the Logical Observation Identifiers Names and Codes (LOINC) were used for the lipase measurement but since these codes are only available for a subset of patients in Marketscan and Optum databases, to accommodate database needs, the equivalent Current Procedural Terminology (CPT) codes were added to the algorithm. This modified algorithm is:

- The presence of an acute pancreatitis diagnosis from any of the inpatient (not restricted to the primary diagnosis), outpatient, or emergency contacts diagnoses (ICD-9-CM 577.0 or ICD-10-CM K85)

  AND
- A lipase measure within +/- 7 days of the acute pancreatitis diagnosis (using LOINC code of 3040-3 and 2572-6 or CPT code of 83690 for lipase)

  AND
- An abdominal ultrasound (using CPT codes of 76700 and 76705) within +/- 7 days of the acute pancreatitis diagnosis

9.3.2.2 Secondary outcomes

None.

[redacted]

9.3.3 Covariates

Several baseline patient characteristics will be captured in the 6 months prior to the index date. Some of these covariates will be included as covariates in the propensity scores (PS) model.

- Demographics
- Comorbidity indexes: Elixhauser comorbidity index [R14-4775], Charlson comorbidity index
- Diabetes specific complications
- Comorbidities (e.g. CVD [R21-0209])
- Prior/concomitant use of other oral glucose lowering drugs
- Prior/concomitant use of other drug(s) associated with acute pancreatitis [P08-00872]:
    - α-methyldopa, azodisalicylate, bezafibrate, cannabis, carbimazole, codeine, cytosine, arabinoside, dapsone, enalapril, furosemide, isoniazid, mesalamine, metronidazole, pentamidine, pravastatin, procainamide, pyritonol, simvastatin, stibogluconate, sulfamethoxazole, sulinda, tetracycline, valproic acid, all trans-retinoic acid, amiodarone, azathioprine, clomiphene, dexamethasone, ifosfamide, lamivudine, losartan, lynesterol/methoxyethinylestradiol, Mercaptopurine, meglumine, methimazole, nelfinavir, norethindronate/mestranol, omeprazole, premarin, sulfamethazole, trimethoprimsulfamethazole, acetaminophen, chlorthiazide, clozapine, didanosine, erythromycin, estrogen, L-asparaginase, pegasparagase, propofol, tamoxifen, azathioprine, sulfonamides, tetracyclines, alpha-methyldopa
- Prior/concomitant use of other medications (e.g. cardiovascular medications, full list is added in annex 5)
- Other acute pancreatitis risk factors e.g. abdominal surgery, alcoholism and alcohol abuse, cystic fibrosis, gallstones and other gallbladder and biliary tract disorders, hyperparathyroidism, infection, injury to the abdomen, and lupus
- Specific lab test results (when available, see below and SEAP)
- Coronavirus (COVID-19) infection (this is applicable only to patients who have 2020 data) during the baseline period and follow up

Given the nature of the databases, it will not be possible to include exposure to over-the-counter medications as a covariate in the analysis.

The list of covariates is provided in Appendix 5 and all practical definitions and codes can be found in the statistical epidemiological analysis plan (SEAP).

Laboratory test results in a subset of patients:

For a subset of about 40-50% of patients in Optum Clinformatics and 5-15% in MarketScan, laboratory test results are available through linkage with two nationally operating lab test provider chains. Available laboratory test results during the 6 months prior to the index date will be identified using LOINC codes. After PS matching, if major imbalance is observed, patient characteristics with and without lab test results might be further explored as optional additional analysis.
In case of multiple values available for a specific lab result, we will only consider the closest to the date of drug initiation. Laboratory tests of interests are provided in Annex 5 and include amylase (U/L); lipase (U/L); white cell count (G/L); red cell count (T/L); haemoglobin (g/L); haematocrit (%); thrombocyte (G/L); C-reactive protein (mg/L); creatinine (µmol/L), urea (mmol/L); serum bilirubin (µmol/L); GGT (mmol/L); GOT (mmol/L); GPT (mmol/L); ALP (mmol/L); uric acid (mmol/L); cholesterol (HDL, LDL) (mmol/L); triglycerides (mmol/L); serum protein (g/L); albumin (g/L)., C-peptide (pmol/L); HgbA1C (%); OGTT test glucose (mmol/L) and insulin level (pmol/L) at 0, 60 and 120 min [R20-3572].

9.4 DATA SOURCES

Two large US claims databases (Truven Marketscan Commercial Claims and Encounters (CCAE), Truven Marketscan Medicare Supplemental (MDCR), and Optum Clinformatics® Data Mart [CDM]) will be used in this study. Meta-analysis of the 2 databases might be used, when appropriate, to achieve the required study size.

Main data elements from each database that will be used in this analysis include: 1) enrolment records, 2) pharmacy dispensing claims (dispensing date, National Drug Code [NDC] to determine product prescribed, quantity, and days of supply, and 3) medical claims (service date, diagnosis codes [ICD-9-CM, ICD-10-CM], procedure codes [Current Procedural Terminology (CPT)-4, ICD-9 Procedure Coding System (PCS), ICD-10-PCS], and laboratory test results (when available).

9.5 STUDY SIZE

All patients with T2DM who newly initiate therapy with empagliflozin or study comparator who meet the inclusion and exclusion criteria will be included in the analysis.

Event rate of acute pancreatitis reported in patients with T2DM who are treated with canagliflozin was reported to be 2.2 per 1000 PY [RRA-21430]. This rate was used for sample size calculation using the formula of Farrington and Manning (maximum likelihood method) [R14-3295].

Null hypothesis H0: $\pi_2 / \pi_1 \geq 1.5$ (non-inferiority)

A single stage (fixed sample size) design was chosen.

For specified $\alpha = 0.05$ and rates $\pi_1 = 0.0022$ and $\pi_2 = 0.0022$ (odds ratio of 1.000) the power (1 - β) is 80.0% if the test stages consist of the sample sizes given in the last two columns of Table 1.
The computation assumes an allocation ratio (n2/n1) = 1 (Table 1). It is assumed that all patients have 1 year of follow up.

Table 1 Number of empagliflozin initiators and empagliflozin-exposed person-years needed to detect a HR of 1.5 and 2.0 with a power of 80% and □ = 0.05 under 1:1 matching ratio

Hazard ratio (HR)	Information rate	Bunds accept H_0	Bunds reject H_0	sign.level one-sided	α spent	β spent	power achieved	Observations per exposure group	Overall observations
1.5	1.0	1.645	1.645	0.0500	0.0500	-	0.8000	34585.4	69170.8

ADDPLAN Adaptive Design Software 2019 and SAS 9.4 software [redacted]) were used to calculate the sample size.

Analysis of this study will be initiated as soon as a sufficient sample size to exclude a HR of 1.5 with 80% power is reached. Based on a feasibility assessment conducted in Optum and MarketScan databases using data between 1 August 2014 and the latest data-cut available in MarketScan (30 September 2020) and Optum (31 March 2021), the dual-therapy cohort was reported with the highest number of empagliflozin initiators, therefore meta-analysis of the dual therapy cohorts including the data from the MarketScan and Optum databases will be the main analysis of this study as it will be the only powered analysis.

9.6 DATA MANAGEMENT

Data for this study is stored using the secured Instant Health Data (IHD) platform (https://www.bhei.com/product). Access to the data is granted by password to trained, BI personnel only. Full details of the data management plan are documented in a separate NIS-Data Management and Review Plan (NIS-DMRP).

9.7 DATA ANALYSIS

The statistical analysis of this study is summarized below. Full details of the statistical analysis will be documented in the SEAP, which will be finalized before the start of data analysis. The final study cohorts will be created using the IHD platform and all analyses will be performed using SAS software ([redacted]

9.7.1 Definitions

- Index date: Date of the first recorded claim for a qualifying prescription of an index medication as a new user.

- Follow-up: Starts from the day after the index date until the first qualifying event has been met (see Table 2 and 3).
- Look-back period: Patients are required to have at least 6 months of continuous registration in the database prior to initiation of an index medication. The look-back period is defined as 6 months prior to the index date and including the index date. The look-back period was specified to confirm new medication use (i.e. having a first prescription claim for empagliflozin or other oral non-incretin/non-SGLT2i-containing hypoglycaemic without use of these medications in the prior 6 months) and describe baseline parameters, such as prior medical history and medications.
- Grace period: 30 days in main analysis [c18659315-02] and 90 days [R18-1760, RRA-21430, P20-07536] in sensitivity analysis.

Table 2 Definitions for study end date

Reason for End of Study or censoring (earliest date of options below)	**Definition for End Date**
Acute pancreatitis event	Date of the first acute pancreatitis using ICD9 or ICD10 codes
Switch of index medication to another hypoglycaemic agent; see Table 3	Last date of known prescription coverage (date of last prescription fill plus days' supply minus one day) and a grace period equal to 30 days. Exposure time will not extend past the date of the first prescription claim for the newly prescribed agent*
Addition of incretin-based therapy (with continuation of index therapy)	Date of the prescription claim for the added incretin therapy
Addition of SGLT2i (with continuation of index therapy)	Date of the prescription claim for the added SGLT2i therapy
Addition of insulin (with continuation of index therapy)	Date of the prescription claim for the added insulin therapy
Addition of the within treatment line comparator index drug; see Table 3 (with continuation of index therapy)	Date of the prescription claim for the added treatment line comparator index drug
Discontinuation of index drug	Last date of known prescription coverage (date of last prescription fill plus days' supply minus one day) and a grace period equal to 30 days*
End of study data	Date of death#, Date of end of registration, Date of Study End

*The last date of known coverage may also be extended further to account for overlap periods – when a prescription is refilled before the previous supply was considered exhausted. Gaps between coverage and prescription refills that are less than the duration of each patient's respective grace period will be considered continuous exposure time.

#It is not typically possible to ascertain all deaths that occur in studies based on administrative claims data.

Discontinuation, addition, and switching are defined in the SEAP. Considerations for the follow up time and censoring after switching or addition are presented in Table 3.

Index drug for the monotherapy are empagliflozin and metformin, for the dual therapy empagliflozin and SU, and for the triple therapy cohort empagliflozin and TZD.

Table 3 Considerations for switching or adding during the follow-up period

Treatment Line	**Index Drug**	**Can Add (i.e. do not censor)**	**Cannot Add (i.e. censor at switch/addition)**
Monotherapy	Empagliflozin	SU, TZD, and medications not mentioned in the next column	Metformin, incretins*, other SGLT2i, Insulin
	Metformin	SU, TZD, and medications not mentioned in the next column	Any SGLT2i, incretins*, Insulin
Dual Therapy	Empagliflozin	TZD, and medications not mentioned in the next column	SU, incretins*, other SGLT2i, Insulin
	SU	TZD, and medications not mentioned in the next column	Any SGLT2i, incretins*, Insulin
Triple Therapy	Empagliflozin	Medications not mentioned in the next column	TZD, incretins*, other SGLT2i, Insulin
	TZD	Medications not mentioned in the next column	Any SGLT2i, incretins*, Insulin

*Incretins = DPP-4i or GLP-1 RA.

In the dual therapy and triple therapy cohorts, if patients discontinue or switch medications other than index medication (e.g. metformin in the dual therapy cohort, and SU or metformin in the triple therapy cohort) they will not be censored; however, in the sensitivity analysis, this will be assessed by censoring those patients. Definitions for discontinuation, switch, and addition are mentioned in the SEAP.

9.7.2 Propensity score approach

Decisions to begin a specific hypoglycaemic agent are influenced by demographic, medical, and clinical factors, and same factors might be associated with the outcomes of interest. The propensity score is the predicted probability of being assigned to a particular treatment conditional on a set of observed covariates. Because the models predict the probability of being treated with the exposure drug and not the probability of experiencing the outcome, a high number of variables can be used in the predicting regression model [P12-04844, R14-5241, R14-5284, R14-5389].

Propensity scores for the comparison of empagliflozin vs. study comparator will be generated. Furthermore, given the different inclusion/exclusion criteria used for each treatment line cohort, the propensity scores will be cohort specific (i.e., propensity scores will be calculated for the monotherapy, dual therapy and triple therapy cohorts separately).

As a first step, a propensity score is estimated for each cohort member at the index date, based on the values of the observed covariates during the look-back period. In this study, propensity scores will be estimated by conducting multivariable logistic regression modelling and incorporating measured potential predictors of therapy as independent variables and exposure group status (empagliflozin group vs. comparator) as the outcome.

We will use PS matching to balance a number of covariates. Key advantages of PS matching are that large numbers of covariates can be adjusted even when studying infrequent outcomes, the achieved covariate balance can be documented, multiple outcomes can be studied after a single matching process, [R13-1120] and patients who cannot find comparable pairs will be implicitly dropped out of the analysis increasing the validity of findings [R17-1404].

The propensity score will be used to match patients in a 1:1 ratio using a nearest-neighbor algorithm and calipers of width equal to 0.2 of the standard deviation of the logit of the estimated propensity score [R13-3590, R18-2599, R16-1227]. A 1:n variable ratio matching will not be used as it involves several complications while providing only a minimal gain in estimation precision [R17-1267]. If balance is not achieved, the PS model will be refitted using interaction terms [R18-2599]. PS balance achievement will be inspected by tabulating all patient characteristics by treatment status and by assessing the standardized differences. Any patient characteristics with a standardized difference of >10% will be considered for additional post-matching adjustment [R13-3590].

With the publication of EMPA-REG OUTCOME trial results in September 2015 and the approval of a separate indication to reduce the risk of cardiovascular death in adults with T2DM and established cardiovascular disease by the US FDA in December 2016, the characteristics of patients initiating empagliflozin has likely changed during the study period. To account for patient characteristics changing over time, patients will be matched on the calendar quarter-year of initiation of the study medication. If we lose too many patients using this method, we may instead decide to match on year of initiation of index medication and then include calendar quarter-year variable in the PS model.

9.7.3 Main analysis

The study will be conducted utilizing a modified “as-treated” approach. Users of empagliflozin or a comparator oral non-incretin/non-SGLT2i–containing hypoglycaemic agent will be considered exposed from the date of first prescription claim until earliest claim for acute pancreatitis or until one of the following censoring criteria have been met (Table 3):

- The date of end of continuous registration in the database
- The date of death
- The date of study end
- The date of discontinuation of index medication (defined as the date of the last date of last dispensing + days supply + grace period). The grace period is a time period after exposure end during which observed outcomes are still attributed to the exposure. Grace

period varies according to the specific outcome. In this study, for acute pancreatitis, we have 30 days grace period in the main analysis [c18659315-02] and 90 days in the sensitivity analysis [R18-1760, RRA-21430, P20-07536].

- The date of switch of index medication to another hypoglycaemic agent
- The date of addition of incretin-based therapy (with continuation of index therapy)
- The date of addition of SGLT2i (with continuation of index therapy)
- The date of addition of insulin (with continuation of index therapy)
- The date of addition of the within treatment line comparator index drug (with continuation of index therapy)

For those who switch to an incretin therapy/SGLT2i, or switch to the within treatment line comparator, exposure duration will include the last date of known prescription coverage before the switch. For discontinuation of the index drug (with no prescription claim for a new hypoglycemic drug), exposure duration will include the last date of known prescription coverage (date of last prescription fill plus days' supply minus one day) and a grace period equal to 30 days. The last date of known coverage may also be extended further to account for overlap periods – when a prescription is refilled before the previous supply was considered exhausted. Gaps between coverage and prescription refills that are less than the duration of each patient's respective grace period will be considered continuous exposure time. For patients who switch, exposure time will not extend past the date of the first prescription claim for the newly prescribed switch agent.

For patients who add an incretin-based therapy, SGLT2i, or a within treatment line comparator index drug, their data will be censored on the date of the prescription claim for the added medication.

Patients with chronic use of insulin at baseline (see SEAP for definition) in the outpatient setting during the follow-up period will be censored from the study.

From a feasibility assessment conducted in November 2021, it is known that there are not enough study participants in the Optum and MarketScan database in each therapy line and the dual-therapy cohort was reported with the highest number of empagliflozin initiators. Therefore, a meta-analysis of the dual therapy cohorts including the data from the Marketscan MarketScan and Optum databases will be the main analysis of this study

Meta-analysis of different treatment line cohorts with the different comparators (first, second and third line) will not be conducted in this study as patients in these 3 cohorts will likely have very different profiles including different disease stages, and results would be difficult to interpret.

The incidence rates (per 1000 PY) and corresponding 95% confidence intervals (CI) of acute pancreatitis during the follow-up time will be calculated in each exposure group of interest in the unmatched and PS-matched cohorts.

All results will be presented for each database separately but if there is not enough sample size in each treatment line cohort in each database, after evaluating potential heterogeneity, meta-analysis techniques will be used to pool the 2 treatment line cohorts of the 2 databases. Descriptive tables and all parameter estimates from the main and all sensitivity analyses will be pooled using meta-analytic methods assuming a fixed effects model, to avoid potential biases associated with random effects pooling in the context of few databases [R17-1410].

Cox proportional hazards regression models based on time-to first acute pancreatitis event will be used to estimate hazard ratios (HR) and 95% CIs for each treatment line comparison of interest (in each database or in case of limited sample size a meta-analysis of 2 databases) in the unmatched and PS-matched cohorts. Proportionality hazard assumption will be checked using the log rank test.

9.7.4 Meta-analysis

After evaluating potential treatment effect heterogeneity we may pool results from the two databases. Descriptive tables and all parameter estimates from the main and all sensitivity analyses will be pooled using meta-analytic methods assuming a fixed effects model, since random effects pooling can be biased in the context of few databases [R17-1410]. Calculation of an overall mean/proportion/hazard ratio from two databases reporting a single mean/proportion/hazard ratio will use the inverse variance method for pooling [R02-0971].

To correct variance for potential duplicates in pooling two databases for the primary outcome, the following method will be used. The variance correction for overlapping samples when pooling multiple databases was described by [redacted] and [redacted] [M20-0016].

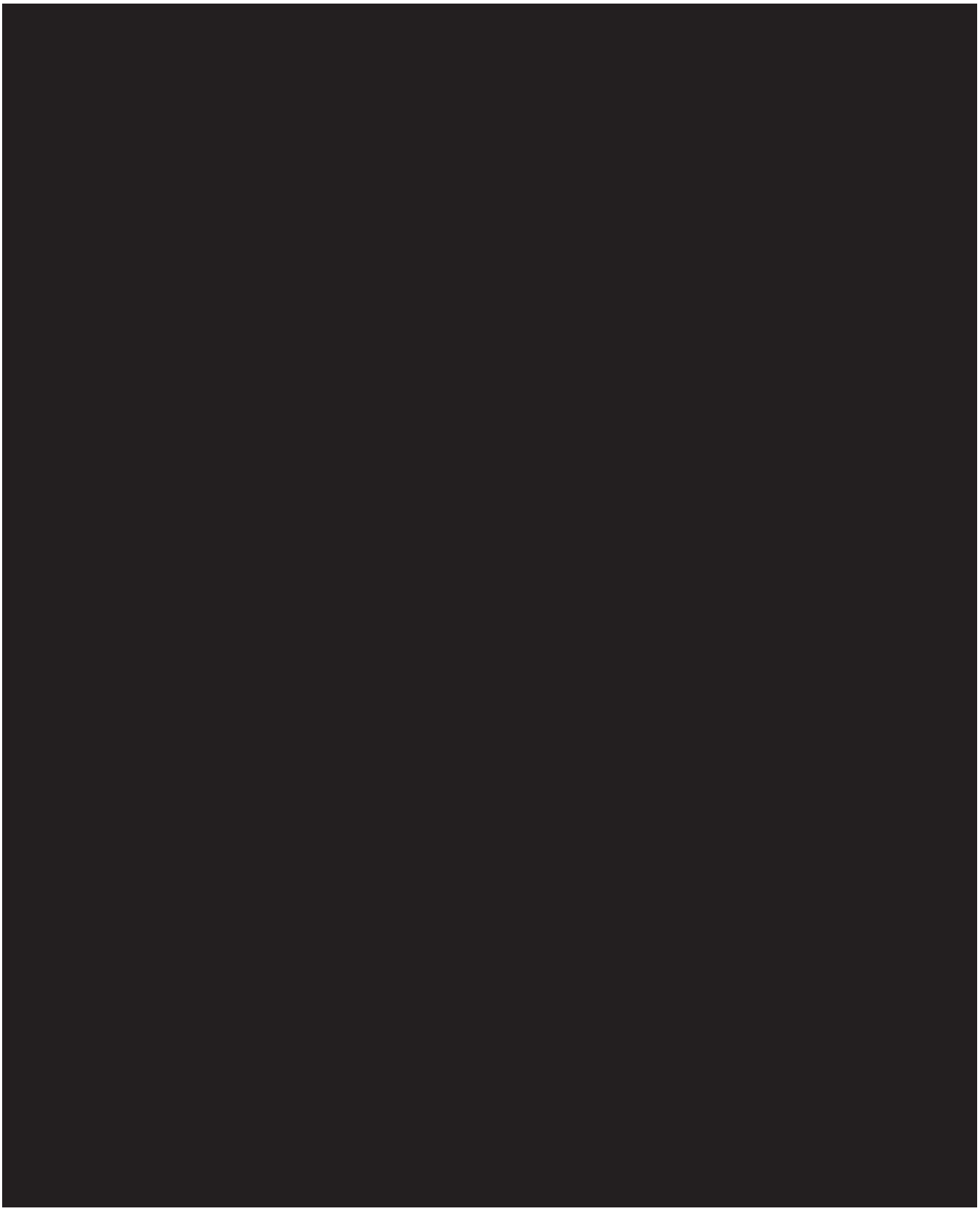
The formula for the variance is given by

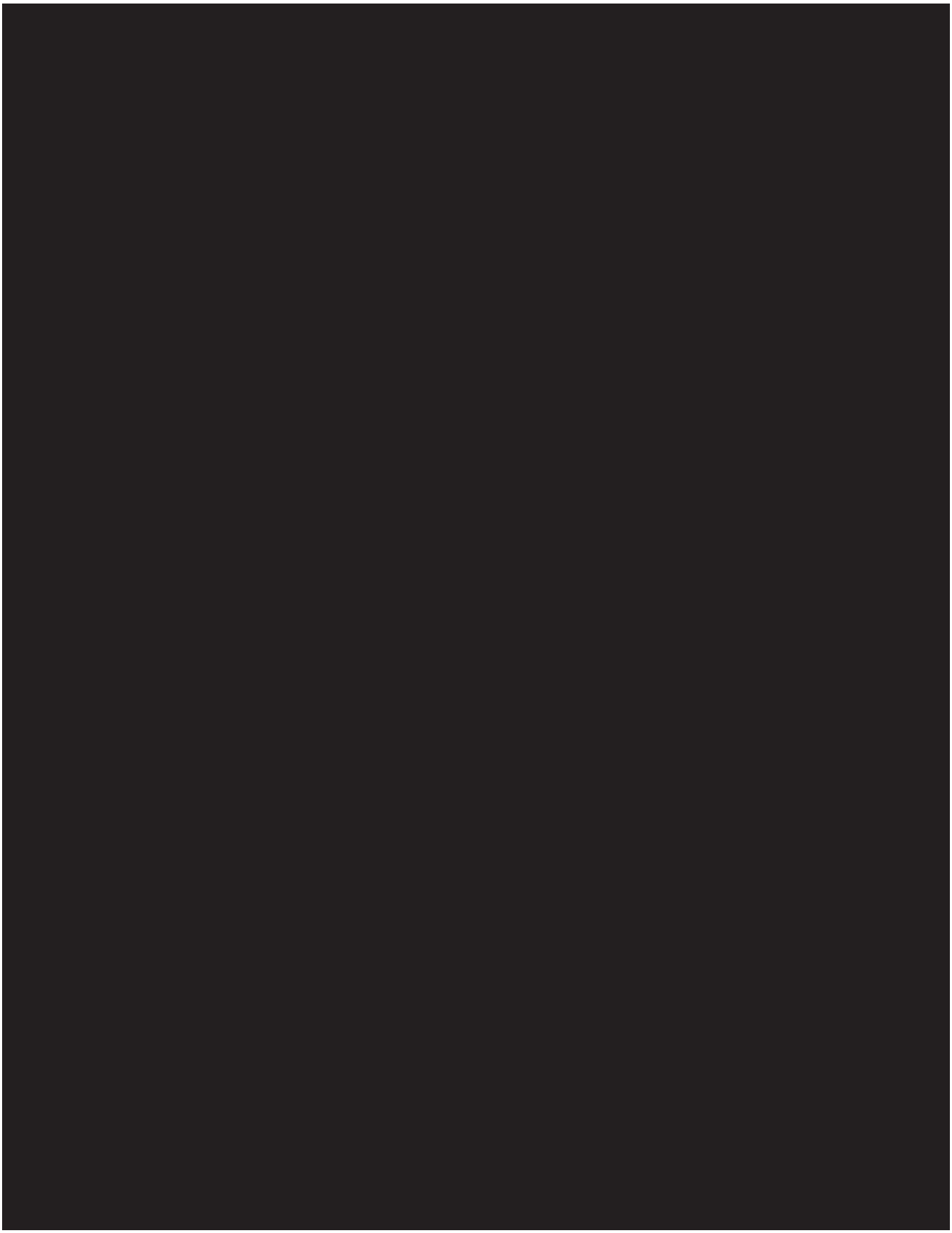
$$\hat{\sigma}^2_{combined} = w_1^2\hat{\sigma}_1^2 + w_2^2\hat{\sigma}_2^2 + 2w_1w_2\rho\hat{\sigma}^2$$

Where

- w_1 and w_2 are the weights applied to the two databases and $w_2 = 1 - w_1$
- $\hat{\sigma}_1^2$ and $\hat{\sigma}_2^2$ are the variance estimates from both databases
- ρ is the % of overlapping observations in the smaller dataset
- $\hat{\sigma}^2 = (n_1\hat{\sigma}_1^2 + n_2\hat{\sigma}_2^2)/2$ where n_1 and n_2 are the number of observations in both databases

Given that an exact overlap is not known between databases, estimates in 10% intervals will be used to assess varying degrees of variance in the pooled point estimates. The pooled analyses will be conducted using R package **rmeta** in R studio [R20-1986, M20-0016].





[redacted]

9.7.6 Sensitivity analysis

At least the following sensitivity analyses will be performed:

1. All analyses will be performed using an alternate outcome definition using the primary hospitalization discharge diagnosis only (ICD-9-CM 577.0 or ICD-10-CM K85 acute pancreatitis).
2. Exclude cases with ICD-10 K85.2x (Biliary acute pancreatitis) and K85.3x (Alcohol induced acute pancreatitis) and also report the percentage of these cases in overall identified acute pancreatitis cases.
3. Implement an intention-to-treat approach, where all users maintain assignment to their original treatment arm throughout a fixed follow-up period 12 months after first exposure. Users of empagliflozin or a comparator oral non-incretin/non-SGLT2i–containing glucose lowering drugs will be considered exposed from the date of first prescription claim (following a 6-month period without a prescription claim for their index medication) until earliest claim for acute pancreatitis or until one of the following censoring criteria have been met: death, end of registration, or study end. In this analysis, patients discontinuing therapy will not be censored.
4. Subgroup analyses will be performed focusing on patients with and without history of eCVD in the 12 months prior to the index date
5. It is known that Diabetic ketoacidosis (DKA) can be complicated with pancreatitis. As a sensitivity analyses, cases with prior DKA will be excluded.
6. In dual or triple therapy cohorts when the non-index medication (metformin) is discontinued or switched patients will be censored.
7. Considering grace period of 90 days for all medications.

9.7.7 Handling of missing values

The absence of a code for a condition will be interpreted as an absence of the event. If a study variable is totally missing from a database, it is excluded from the analysis of the pooled data. If a variable is missing for only some of the patients a missing data category will be added and utilized in the analysis.

9.7.8 Safety Analysis

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

9.8 QUALITY CONTROL

The quality control, review, and monitoring plan are summarized below. Greater details are documented in the NIS-DMRP.

All measures created, cohorts developed, statistical analyses implemented, and tables completed will be conducted by two analysts independently. After completing the whole analysis, each analyst will undergo quality control review for the other analyst's work. The final results need to be consistent results from both analysts.
This protocol will be strictly followed in the study. All changes to this protocol will be documented in protocol amendments.

All programs for data management and data analyses written by study statistician(s) will be self-documenting with comments about the data handling process, the population selection and the analysis performed by the program. The documentation will be sufficient for another statistician to be able to repeat the program. A statistician other than the one who writes the program will carry out quality control checks of these programs. The programming quality control (QC) will be performed for all programs related to the database, its individual datasets from different registers and statistical analyses. The QC will be documented with the following information:

- Name of the program
- Purpose of the program
- Name of the programmer
- Validation status and date of validation
- Updates and dates of updates
- Name of the QC statistician
- QC findings or comments
- Date of QC

The statistician responsible for the QC of a program will ensure that:

- The correct dataset and population is used
- The analysis is carried out according to the SEAP
- The analysis results are consistent
- The output is in line with the table shells in the SEAP
- The analysis can be interpreted in both statistical and clinical terms

All QC findings by the QC statistician will be documented, and corrections are made to the programs accordingly. All changes are documented as updates to the original program.

The raw dataset and statistical programs used for generating the data included in the final study report will be kept in electronic format and be available for auditing and inspection.

9.9 LIMITATIONS OF THE RESEARCH METHODS

There are several methodological challenges when conducting epidemiologic studies to evaluate the association between glucose lowering drugs and outcomes of interest among patients with diabetes. These challenges include, but are not limited to, changes in treatment in response to advancing diabetes or due to adverse effects of specific drugs and time-varying

risk of an outcome [P12-13528, P14-17457, R14-4378]. Other limitations of the study are listed below.

9.9.1 Data source

The source claims data include limitations with respect to certainty of the capture of exposure, covariates, and outcomes. As a comprehensive insurance database, essentially all billable medical services will result in claims for reimbursement, so that the certainty of capture is tied to likelihood of a claim being submitted to the insurer.

Although duration of diabetes may represent a risk factor for the study outcome, this covariate will be incompletely captured since the patient history in the dataset is relatively short (at least 12 months, and an average of approximately 2 years), and a first claim within the database may not represent diabetes onset since the condition can be latent for some time and is typically not treated with hypoglycaemic medications at its diagnosis.

New initiators are operationally defined as patients with no use in the prior 6 months. This does not ensure, however, that patients have never used the drug of interest; the possibility remains that these patients were treated at some prior time point before they enrolled in their insurance plan.

There is potential for misclassification of dose based on healthcare utilization data, but the "days supply" field is expected to be fairly accurate. Similar concern may be present for exposure classification as well, but we expect the drug codes utilized in the data sources will appropriately represent the drug that is being classified.

Medication use in administrative healthcare databases is restricted to prescription drug medication. Consequently, the use of over-the counter (OTC) medications (e.g., OTC aspirin) is not captured. Additionally, the indication of a claim for prescription medications does not confirm whether the medication was actually taken by the patient or taken as prescribed.

It is estimated that two databases (MarketScan and Optum CDM) have about 10-15% overlap and it is not possible to identify duplicates and remove them between the two databases because patients are de-identified. It is not expected that this overlap impacts the results of this study because it will be much smaller in the study population. Furthermore, there is a sensitivity analysis to consider several scenarios of overlap in patients between the MarketScan and Optum (e.g., 0%, 10%, 20%, etc.), and 95% CIs of primary outcome will be adjusted accordingly.

Given that MarketScan and Optum CDM are claims databases, clinical laboratory data is only available for a small portion of enrolees (approximately 40-50% in Optum CDM and about 5% in [redacted] MarketScan).

9.9.2 Confounding

A strength of this active-comparator new-user (rather than non-user) design is that it mitigates much of the confounding bias that can be prominent in comparative observational studies. Although use of propensity scores will facilitate the control of measured confounders, unmeasured and unidentified confounders could still introduce bias if they are differentially distributed among the exposed and comparator groups and are related to the outcome. As an example, use of over-the-counter medications will remain unmeasured in this study.

Confounding by indication or severity, also known as channelling bias, is a common bias in pharmacoepidemiology. Patients starting treatment with a newly marketed drug might have more severe disease than patients not taking the medication either because of self-selection or because of physician preference. They may also have a less severe form of the disease if physicians prefer to test new drugs with a less familiar safety profile in less severely affected patients. New medications may also be prescribed differentially by physicians who are "early adopters" of new technologies and who systematically treat more severely affected patients with the new medications. In previous empagliflozin safety studies, DPP-4 inhibitors were selected as the comparator group because these group of medications (relative to other oral hypoglycemic agents such as metformin and sulfonylureas) were recently introduced in the market. Therefore, using them as comparators reduces the risk of this type of bias. However, in this study, because of the existing association between DPP4 initiators and GLP1 agonists and study outcome (acute pancreatitis), these medications were not selected as comparators. Because of the possibility of channeling bias, the remaining oral hypoglycemic agents (metformin, SU, TZD) were not appropriate for a new user design that utilized a combined comparison group. A prevalent new user design was considered for this study, but because the long-term history of therapies for prevalent users is not typically available in the US claims databases, it was deemed more appropriate to use the active comparator new user design based on treatment lines as mentioned in section 9.3.1.

Study participants in the empagliflozin group will be 1:1 matched with comparators to account for confounders. After PS matching, study participants will be matched based on the calendar quarter year of the cohort entry to help minimize residual confounding.

Although we will try to measure and include all available confounders in the PS models, some important variables e.g. alcohol abuse or smoking which are correlated with the outcome are not available for all study participants. Furthermore, study participants in the comparator groups are probably more prone to have lower socioeconomic status which is a potential for channelling bias that is not easy to detect in our study. These patients may also have different background risk for alcohol use and smoking.

Some of the outcome risk factors, e.g. infection, are only captured via hospital admission claims. Therefore, infections not resulting in hospitalization cannot be captured in this study and this increases the risk of residual confounding.

9.9.3 Misclassification

To minimize misclassification of the recorded patient characteristics, previously validated algorithms or code-lists will be used whenever available. Code-lists were reviewed by qualified medical reviewers prior to implementation. A preliminary study to optimize and validate the algorithm for identification of cases of acute pancreatitis using ICD-9-CM and ICD-10-CM codes was conducted in the [redacted]

Some of the major risk factors for acute pancreatitis (e.g. alcohol use, obesity, biliary pathology not requiring reimbursement) are under-reported in claims databases. A similar limitation exists for use of medications known to cause acute or chronic pancreatitis, and it is impractical to account for all of these, even if the data are available. Conversely, the incidence of acute pancreatitis can be overestimated because providers may have used the acute pancreatitis code, abdominal ultrasound or serum lipase measurement to rule out the diagnosis of acute pancreatitis. To mitigate this risk, diagnosis for acute pancreatitis will be assessed using an algorithm that has been validated in the [redacted] and shown to have a sensitivity of 89.8% and a specificity of 79.4% [R20-3554]. However, this algorithm does not allow for etiological or pathophysiological description of the type of acute pancreatitis.

Further, the study utilizes a modified as-treated approach as the primary analysis, which could result in exclusion of some cases of acute pancreatitis due to censoring criteria (i.e., patients would be classified as not experiencing acute pancreatitis, but the event could have occurred after censoring). In order to address this, we will perform a sensitivity analysis using an ITT approach. This approach is more conservative and maintains drug classification similar to randomization; however, there is greater risk of exposure misclassification. Ultimately, however, this method will allow for evaluation of potentially additional cases of acute pancreatitis that transpire during the study period given the more limited censoring criteria.

Pancreatitis reoccurs in up to 25% of patients following hospital admission for their first episode of acute pancreatitis, with smoking and/or alcohol abuse demonstrated as predominant risk factors. Smoking and alcohol use could not be measured properly in the US claims databases. Moreover, the baseline period is only 6 months which might result in misclassification of some of recurrent acute pancreatitis events as the first event.

Another important topic to take into account is death which is considered a censoring event, but this information is not well captured in claims databases.

9.9.4 COVID-19 considerations

Although, there are a lot of unknown details around COVID-19 complications, a few small studies (mainly case reports) reported a possible link between COVID-19 infection and developing acute pancreatitis [R20-1531, R20-1532, R20-1536, R20-3357]. However, two recent observational studies conducted in the Netherlands and Italy suggested that the incidence of acute pancreatitis, as complication of COVID-19 infection, is very low and no

clear etiology was reported [R21-1729, R21-1730]. Therefore, as an optional analysis, characteristics of patients with acute pancreatitis which were observed after Q1 2020 in these 2 databases will be evaluated to see if we can find any COVID-19 codes in the month prior to acute pancreatitis.

9.9.5 Generalizability

Using a PS-matched analysis within a new user active comparator design decreases channelling bias, but also decreases the representativeness of the final patient cohort. The findings might not be generalizable to all patients with T2DM, especially those on treatment regimens that will not be included in this analysis.

The use of large claims data sources, such as MarketScan and Optum CDM, helps to ensure good representativeness of the US population. Although people over 65 years are under-represented in the MarketScan databases, the use of the Optum CDM data will increase the proportion of people older than 65 years in the analysis.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRBs) / Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

9.10.2 Study records

9.10.2.1 Source documents

Not applicable.

9.10.2.2 Direct access to source data and documents

Not applicable.

9.10.3 Protocol deviations

None.

9.10.4 Compensation available to the patient in the event of study related injury

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, Guidelines for Good Pharmacoepidemiology Practice (GPP), and the relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic,

diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be registered with European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and on clinicaltrials.gov.

Data are de-identified and comply with the Health Insurance Portability and Accountability (HIPA) Act [R19-2252], and because this study will not involve the collection, use, or transmittal of individually identifiable data, Institutional Review Board review or approval is not required.

10.2 STATEMENT OF CONFIDENTIALITY

Not applicable.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The principal and co-investigators will lead the development of scientific manuscript(s) of the results to be published. A summary of the main results of the study, whether positive or negative, will always be made available to the public. As per Section V of *Guidelines for Good Pharmacoepidemiology Practices* [R11-4318] and the *Guideline on Good Pharmacovigilance Practices*, Module VIII, Section B.7 [R13-5420], the outcome of a study will always be presented in an objective and truthful manner providing a comprehensive and accurate description of the findings. In no way shall the interpretation and presentation of the results be aimed towards any commercial, financial or personal interests.
The principal and co-investigators will write the study report and the results will be reported within the earliest Periodic Benefit Risk Evaluation Report (PBRER). The study results will be published in the EU PAS registry.

13. REFERENCES

13.1 PUBLISHED REFERENCES

R10-6620	Girman CJ, Kou TD, Cai B, Alexander CM, O'Neill EA, Williams-Herman DE, Katz L. Patients with type 2 diabetes mellitus have higher risk for acute pancreatitis compared with those without diabetes. Diab Obes Metab 2010; 12: 766-771.
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.
R10-2088	Noel RA, Patterson RE, Braun DK, Bloomgren GL. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes. Diab Care 2009; 32: 834-838.
R18-1760	Hong JL, Buse JB, Jonsson Funk M, Pate V, Sturmer T. The Risk of Acute Pancreatitis After Initiation of Dipeptidyl Peptidase 4 Inhibitors: Testing a Hypothesis of Subgroup Differences in Older U.S. Adults. Diabetes Care. 2018;41(6):1196-1203.
P19-09574	Azoulay L, Filion KB, Platt RW, et al. Association Between Incretin-Based Drugs and the Risk of Acute Pancreatitis. JAMA internal medicine. 2016;176(10):1464-1473.
R13-3873	Wenten M, Gaebler JA, Hussein M, Pelletier EM, Smith DB, Girase P, Noel RA, Braun DK, Bloomgren GL. Relative risk of acute pancreatitis in initiators of exenatide twice daily compared with other anti-diabetic medications: a follow-up study. Diabet Med 2012; 29: 1412-1418.
R11-0776	Dore DD, Bloomgren GL, Wenten M, Hoffman C, Clifford CR, Quinn SG, Braun DK, Noel RA, Seeger JD. A cohort study of acute pancreatitis in relation to exenatide use. 2011 Diab Obes Metab 2011; 13: 559-566.
R19-3424	Li X, Zhang Z, Duke J. Glucagon-like peptide 1-based therapies and risk of pancreatitis: a self-controlled case series analysis. Pharmacoepidemiology and drug safety. 2014;23(3):234-239.
P13-04390	Singh S, Chang H-Y, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike Peptide 1-Based Therapies and Risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus. JAMA Intern Med 2013; doi:10.1001/jamainternmed.2013.2720.
P13-16900	Funch D, Gydesen H, Tornoe K, Major-Pedersen A, Chan KA. A

	prospective, claims-based assessment of the risk of pancreatitis and pancreatic cancer with liraglutide compared to other antidiabetic drugs. Diabetes, obesity & metabolism. 2014;16(3):273-275.Romley 2012
P17-03843	Knapen LM. Essen JHM, Leufkens HB, van Erp NP, Keulemans YC, deJong RGPJ, de Vries F, de Bruin ML, Croes S. Use of incretin agents and risk of acute and chronic pancreatitis: a population-based cohort study. Diabet Obes Metab 2017; 19: 401-411.
P14-06737	Faillie JL, Azoulay L, Patenaude V, Hillaire-Buys D, Suissa S. Incretin based drugs and risk of acute pancreatitis in patients with type 2 diabetes: cohort study. Bmj. 2014;348:g2780.
P15-05208	Thomsen RW, Pedersen L, Moller N, Kahlert J, Beck-Nielsen H, Sorensen HT. Incretin-based therapy and risk of acute pancreatitis: a nationwide population-based case-control study. Diabetes Care. 2015;38(6):1089-1098.
R19-3425	Shen H-N, Chang Y-H, Chen H-F, Lu C-L, Li C-Y. Increased risk of severe acute pancreatitis in patients with diabetes. Diabet Med 2012; 29: 1419-1424
R19-3426	Kim YG, Kim S, Han SJ, Kim DJ, Lee KW, Kim HJ. Dipeptidyl Peptidase-4 Inhibitors and the Risk of Pancreatitis in Patients with Type 2 Diabetes Mellitus: A Population-Based Cohort Study. Journal of diabetes research. 2018;2018:5246976
R19-3427	Chang CH, Lin JW, Chen ST, Lai MS, Chuang LM, Chang YC. Dipeptidyl Peptidase-4 Inhibitor Use Is Not Associated With Acute Pancreatitis in High-Risk Type 2 Diabetic Patients: A Nationwide Cohort Study. Medicine. 2016;95(7):e2603.
R19-3428	Yabe D, Kuwata H, Kaneko M, et al. Use of the Japanese health insurance claims database to assess the risk of acute pancreatitis in patients with diabetes: comparison of DPP-4 inhibitors with other oral antidiabetic drugs. Diabetes, obesity & metabolism. 2015;17(4):430-434.
R19-3429	Liao KF, Lin CL, Lai SW, Chen WC. Sitagliptin use and risk of acute pancreatitis in type 2 diabetes mellitus: A population-based case-control study in Taiwan. European journal of internal medicine. 2016;27:76-79.
R11-5180	Lai SW, Muo CH, Liao KF, Sung FC, Chen PC. Risk of acute pancreatitis in type 2 diabetes and risk reduction on anti-diabetic drugs: a population-based cohort study in Taiwan. The American journal of gastroenterology. 2011;106(9):1697-1704.
P16-11950	Tseng CM, Liao WC, Chang CY, et al. Incretin-based pharmacotherapy and risk of adverse pancreatic events in the ethnic Chinese with diabetes mellitus: A population-based study in Taiwan. Pancreatology : official journal of the International Association of Pancreatology (IAP) [et al].

	2017;17(1):76-82.
R19-3430	Chou HC, Chen WW, Hsiao FY. Acute pancreatitis in patients with type 2 diabetes mellitus treated with dipeptidyl peptidase-4 inhibitors: a population-based nested case-control study. Drug safety. 2014;37(7):521-528.
R14-1501	Moores K, Gilchrist B, Carnahan R, Abrams T. A systematic review of validated methods for identifying pancreatitis using administrative data. Pharmacoepidemiology and Drug Safety. 2012;21(S1):194-202.
R19-3492	Adamson DM, Chang S, Hansen LG. White Paper: Health Research Data for the Real World: The MarketScan Databases. Available at : https://www.researchgate.net/publication/281570301_Health_research_data_for_the_real_world_The_MarketScan_databases
R19-3491	[redacted]Watson Health. White Paper: The Truven Health MarketScan databases for health services researchers. Available at https://truvenhealth.com/portals/0/assets/2017_MarketScan_Databases_Health_Services_Researchers.pdfAccessed 25 October 2019.
R18-3672	Munch T, Christensen LB, Adelborg K, et al. Positive predictive values of ICD-10 codes to identify incident acute pancreatitis and incident primary malignancy in the Scandinavian national patient registries among women with postmenopausal osteoporosis. Clin Epidemiol. 2017;9:411-9
R19-3493	Optum, Inc. Finding the right patients and investigators for faster clinical trials. Available at https://www.optum.com/content/dam/optum3/optum/en/resources/brochures/wf314692-optum-clinical-trial-solutions-brochure.pdf. Accessed 11 February 2019.
R17-1267	Wang SV, Schneeweiss S, Rassen JA. Optimal matching ratios in drug safety surveillance. Epidemiology 25 (5), 772 - 773 (2014)
R20-0777	Romley JA, Goldman DP, Solomon M, McFadden D, Peters AL. Exenatide therapy and the risk of pancreatitis and pancreatic cancer in a privately insured population. Diabetes Technol Ther. 2012 Oct;14(10):904-11. Epub 2012 Jul 30.
R14-4775	Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005 Nov;43(11):1130-9.
R20-0778	Ahmed Ali U, Issa Y, Hagenaars JC, et al. Risk of Recurrent Pancreatitis and Progression to Chronic Pancreatitis After a First Episode of Acute Pancreatitis. Clin Gastroenterol Hepatol. 2016;14(5):738–746. doi:10.1016/j.cgh.2015.12.040
P12-13528	Lo Re V, 3rd, Haynes K, Ming EE, Wood Ives J, Horne LN, Fortier K, et

	al. Safety of saxagliptin: rationale for and design of a series of postmarketing observational studies. Pharmacoepidemiol Drug Saf 2012; 21 (11): 1202-15.
P14-17457	Rawson NS. Review of the quality of observational studies of the association between rosiglitazone and acute myocardial infarction. J Popul Ther Clin Pharmacol 2014; 21 (2): e214-32.
R14-4378	Patorno E, Patrick AR, Garry EM, Schneeweiss S, Gillet VG, Bartels DB, et al. Observational studies of the association between glucose-lowering medications and cardiovascular outcomes: addressing methodological limitations. Diabetologia 2014; 57 (11): 2237-50.
R14-3295	Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med 1990 ; 9(12) ; 1447-1454.
R20-1984	time varying covariates and meta-analysis references to be added
R02-0971	DerSimonian R & Laird N (1986): Meta-analysis in clinical trials. Controlled Clinical Trials, 7,177–88; Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T (2013): Meta-analysis of prevalence. Journal of Epidemiology and Community Health, 67, 974–8
R20-1986	https://cran.r-project.org/web/packages/rmeta/rmeta.pdf
R18-2599	Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011 ; 46; 399-424.
R20-1531	Anand ER, Major C, Pickering O, Nelson M. Acute pancreatitis in a COVID-19 patient. British Journal of Surgery, Online ahead of print, 2020 Apr 27, doi: 10.1002/bjs.11657; 2020. p. e182
R20-1532	Hadi A, Werge M, Kristiansen KT, Pedersen UG, Karstensen JG, Novovic S, et al. Coronavirus disease-19 (COVID-19) associated with severe acute pancreatitis: case report on three family members. Pancreatology, Article in Press, Corrected Proof, Available online 5 May 2020, doi: 10.1016/j.pan.2020.04.021; 2020. p. 665-667.
R20-1533	Rajesh G, Nair AS, Narayanan VA, Balakrishnan V. Acute pancreatitis in viral infections, with possible progression to chronic pancreatitis. Indian J Gastroenterol 2008 ; 27(4) ; 162-164.
R20-1534	Agzarian AE, Agzarian AY. Influenza A as a cause of acute pancreatitis: a case report. Proc UCLA Healthcare 2016 ; 20
R20-3357	Liu F, Long X, Zou W, Fang M, Wu W, Li W, et al. Highly ACE2 expression in pancreas may cause pancreas damage after SARS-CoV-2 infection. doi: 10.1101/2020.02.28.20029181; 2020.
R20-1536	Wang F, Wang H, Fan J, Zhang Y, Wang H, Zhao Q. Pancreatic injury

	patterns in patients with COVID-19 pneumonia. Gastroenterology, Journal Pre-proof, Published online: April 01, 2020, doi: 10.1053/ j.gastro.2020.03.055; 2020. p. 367-370.
P20-07536	Yuan Z, DeFalco F, Wang L, Hester L, Weaver J, Swerdel JN, et al. Acute pancreatitis risk in type 2 diabetes patients treated with canagliflozin versus other antihyperglycemic agents: an observational claims database study. Curr Med Res Opin 2020 ; 36(7) ; 1117-1124.
R14-4278	Schneeweiss S, Rassen JA, Glynn RJ, Myers J, Daniel GW, Singer J, Solomon DH, Kim SY, Rothman KJ, Liu J, Avorn J. Supplementing claims data with outpatient laboratory test results to improve confounding adjustment in effectiveness studies of lipid-lowering treatments. Med Res Methodol 2012 ; 12; 180
R20-3573	Zhang Z, Kim HJ, Lonjon G, Zhu Y, AME Big-Data Clinical Trial Collaborative Group. Balance diagnostics after propensity score matching. Ann Transl Med 2019 ; 7(1) ; 16
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.
R20-3572	Miko A, Eross B, Sarlos P, Hegyi P, Marta K, Pecsi D, et al. Observational longitudinal multicentre investigation of acute pancreatitis (GOULASH PLUS): follow-up of the GOULASH study, protocol. BMJ Open 2019 ; 9; e025500
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.
R20-3555	Nichols GA, Deruaz-Luyet A, Iliev H, Brodovicz KG. Using electronic data to validate acute pancreatitis diagnoses. 36th Int Conf on Pharmacoepidemiology and Therapeutic Risk Management (ICPE 2020 All Access) Virtual, 16 - 17 Sep 2020. Pharmacoepidemiol Drug Saf 2020 ; 29(Suppl 3) ; 301-302.
R20-3554	Nichols GA, Deruaz-Luyet A, Illiev H, Brodovicz KG. Using electronic data to validate acute pancreatitis diagnoses. 36th Int Conf on Pharmacoepidemiology and Therapeutic Risk Management (ICPE 2020 All Access) Virtual, 16 - 17 Sep 2020 (Poster). 2020
R21-0209	Bexelius TS, Ljung R, Mattsson F, Lagergren J. Cardiovascular disease and risk of acute pancreatitis in a population-based study. Pancreas 2013 ; 42(6) ; 1011-1015.
P17-01404	American Diabetes Association. Pharmacologic approaches to glycemic treatment. Diabetes Care 2017 ; 40(Suppl 1) ; S64-S74.
R21-1729	Bulthuis MC, Boxhoorn L, Beudel M, Elbers PWG, Kop MPM, Wanrooij

	RLJ van, et al. Acute pancreatitis in COVID-19 patients: true risk? Scand J Gastroenterol 2021 ; 56(5) ; 585-587.
R21-1730	Troncone E, Salvatori S, Sena G, Cristofaro E de, Alfieri N, Marafini I, et al. Low frequency of acute pancreatitis in hospitalized COVID-19 patients. Pancreas 2021 ; 50(3) ; 393-398.
P08-00872	Badalov N, Baradarian R, Iswara K, Li J, Steinberg W, Tenner S. Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol 2007 ; 5(6) ; 648-661.
P17-07372	Loehr JM, Dominguez-Munoz E, Rosendahl J, Besselink M, Mayerle J, Lerch MM, et al, HaPanEU/UEG Working Group. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United Eur Gastroenterol J 2017 ; 5(2) ; 153-199.
P13-15588	Cohen D. Reports of pancreatitis are 20 - 30 times more likely with GLP-1 drugs, analysis finds. Br Med J 2013 ; 346; f2607.
P16-02537	Hung WY, Lanfranco OA. Contemporary review of drug-induced pancreatitis: a different perspective. World J Gastrointest Pathophysiol 2014 ; 5(4) ; 405-415.
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.
R14-5241	Arbogast PG, Ray WA. Performance of disease risk scores, propensity scores, and traditional multivariable outcome regression in the presence of multiple confounders. Am J Epidemiol 2011 ; 174(5) ; 613-620.
R14-5389	Segal JB, Griswold M, Achy-Brou A, Herbert R, Bass EB, Dy SM, Millman AE, Wu AW, Frangakis CE. Using propensity scores subclassification to estimate effects of longitudinal treatments: an example using a new diabetes medication. Med Care 2007 ; 45(10) (Suppl 2) ; S149-S157.
R13-1120	Schneeweiss S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. Pharmacoepidemiol Drug Saf 2010 ; 19; 858-868.
R17-1404	Sturmer T, Rothman KJ, Avorn J, Glynn RJ. Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution - a simulation study. Am J Epidemiol 2010 ; 172(7) ; 843-854.
R17-1410	Borenstein M, Hedges L, Rothstein H. Meta-analysis: fixed effect vs. random effects. https://www.meta-analysis.com/downloads/M-a_f_e_v_r_e_sv.pdf (access date: 18 April 2017); 2007.

R17-2092	Patorno E, Everett BM, Goldfine AB, Glynn RJ, Liu J, Gopalakrishnan C, et al. Comparative cardiovascular safety of glucagon-like peptide-1 receptor agonists versus other antidiabetic drugs in routine care: a cohort study. Diabetes Obes Metab 2016 ; 18(8) ; 755-765.
R11-2165	Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiol Drug Saf 2006 ; 15; 291-303.
R19-2252	Hansen LG, Chang S. Health research data for the real world: the MarketScan databases. http://truvenhealth.com/portals/0/assets/PH_11238_0612_TEMP_MarketScan_WP_FINAL. pdf (access date: 4 July 2019) ; Truven Health Analytics; 2011.
R11-4318	Guidelines for Good Pharmacoepidemiology Practices (GPP) (revision 2: April 2007). http://www.pharmacoepi.org/resources/guidelines_08027.cfm (access date: 13 September 2011) ; Bethesda: International Society for Pharmacoepidemiology (ISPE); 2007.
R13-5420	European Medicines Agency (EMA) Title: Guideline on good pharmacovigilance practices (GVP): module VIII - post-authorisation safety studies (rev 1) (19 April 2013, EMA/813938/2011 rev 1). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/0 6/WC500129137.pdf (access date: 17 December 2013) ; European Medicines Agency (EMA), Heads of Medicines Agencies (HMA); 2013.
R10-5391	Garg R, Chen W, Pendergrass M. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. Diabetes Care, Publish Ahead of Print, published online August 3, 2010; 2010. p. 2349-2354.
R14-5284	D'Agostino RB. Propensity scores in cardiovascular research. Circulation 2007 ; 115; 2340-2343.

13.2 UNPUBLISHED REFERENCES

RRA-21430	Acute Pancreatitis in patients with T2D who are new users of canagliflozin as compared with new users of other antihypersglycemic agents: a retrospective cohort study using large claims databases in the United States. 01 Jun 2018 ([redacted])
M20-0016	[redacted] Variance of combined effect estimate when samples are not independent. 2014.
c18659315-02	EMPagliflozin compaRative effectIveness and SafEty (EMPRISE) study program. Protocol version 2.0.

14. APPENDICES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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

Study title:
Post-authorization safety study (PASS) to assess the risk of acute pancreatitis in type 2 diabetes mellitus (T2DM) patients newly initiating empagliflozin compared to other oral non-incretin/non-sodium glucose co-transporter-2 inhibitors (SGLT2)-containing glucose lowering drugs

EU PAS Register® number: EUPAS44267
Study reference number (if applicable):

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] 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.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☐	6
1.1.4 Interim report(s)	☐	☐	☒	NA
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:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	NA
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	NA

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, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.3
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.3

[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
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?	☒	☐	☐	9.2.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.2
	4.2.2 Age and sex	☒	☐	☐	9.2.2
	4.2.3 Country of origin	☒	☐	☐	9.2.2
	4.2.4 Disease/indication	☒	☐	☐	9.2.2
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

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)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	NA
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	NA

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.3.1

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

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure 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)	☐	☐	☒	NA

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:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
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)	☒	☐	☐	9.3/9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3/9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3/9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	SEAP
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3
9.3.3 Covariates and other characteristics?	☒	☐	☐	SEAP
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	NA

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

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

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?	☒	☐	☐	9.7
12.1.2 Information bias?	☒	☐	☐	9.7
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).	☒	☐	☐	9.7
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	

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

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?	☐	☐	☒	

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: 29/11/2021

Signature: [redacted]

ANNEX 3. LIST OF ICD 9 AND ICD 10 CODES FOR COHORT CREATION

Condition	ICD 9 codes [1]	ICD 10 codes [2]
T1DM	250.X1, 250.X3	E10.xx
T2DM	250.X0, 250.X2	E11.xx
Gestational diabetes	648.8x	O24.1x, O24.4x
Secondary diabetes	249.xx	E08.xx, E09.xx,E13.xx
Acute pancreatitis	577.0	K85.xx
Chronic pancreatitis	577.1	K86.1 Other chronic pancreatitis
Pancreatitis cancer	157.xx	C25.xx
Other disease of pancreatitis	577.2, 577.8, 577.9	K86.2, K86.3, K86.8x, K86.9

1. 2015 ICD-9-CM Diagnosis Codes: http://www.icd9data.com/2015/Volume1/default htm accessed at 14 March 2020
2. 2019 ICD-10-CM Codes: https://www.icd10data.com/ICD10CM/Codes accessed at 14 March 2020

ANNEX 4. MEDICATION USED TO DEFINE EXPOSURES AND EXCLUSION CRITERIA OR CENSORING

Medication Class / Generic (Brand) Name
Medication for Exposure Groups Definition
Empagliflozin
Empagliflozin (Jardiance): Empa Mono
Empa+ Met
Metformin + Empagliflozin (Synjardy): Empa Dual
Metformin + Empagliflozin extended-release (Synjardy XR): Empa Dual
Metformin
Metformin (Glucophage, metformin hydrochloride, Fortamet, Glumetza, Riomet): Metf Mono
Met + TZD
Metformin + Pioglitazone (Actoplus Met): Metf + TZD
Metformin + Rosiglitazone (Avandamet): Metf + TZD
Met + SU
Metformin + Glipizide (Metaglip): Metformin and SU Dual
Metformin + Glyburide (Glucovance): Metformin and SU Dual
SU (Combine 1st and 2nd gen)
Glimepiride (Amaryl)
Glipizide (Glucotrol)
Glyburide (DiaBeta)
Glynase
Glycron
Micronase
Acetohexamide (Dymelor)
Chlorpropamide (Diabinese)
Tolazamide (Tolinasel)
Tolbutamide (Orinase)
TZD
Alogliptin + Pioglitazone (Oseni)
Pioglitazone (Actos)
Rosiglitazone (Avandia)
SU+ TZD
Glimepiride + Rosiglitazone (Avandaryl)
Glimepiride + Pioglitazone (Duetact)

Medicaiton used in exclusion or censoring exposure duration:
Dipeptidyl peptidase-4 inhibitor (DPP-4i)
Alogliptin (Nesina)
Metformin + Alogliptin (Kazano)
Linagliptin (Tradjenta)
Metformin + Linagliptin (Jentadueto)
Empagliflozin + Linagliptin (Glyxambi)
Saxagliptin (Onglyza)
Metformin + Saxagliptin (Kombiglyze)
Sitagliptin (Januvia)
Metformin + Sitagliptin (Janumet)
Sitagliptin + Simvastatin (Juvisync)
Glucagon-like peptide-1 receptor agonist (GLP-1 RA) with Insulin
Albiglutide (Tanzeum)
Dulaglutide (Trulicity)
Exenatide (Byetta, Bydureon)
Rybelsus (Semaglutide)
Xultophy (insulin degludec and liraglutide injection)
Glargine + Lixisenatide (Soliqua)
Liraglutide (Victoza, Saxenda)
Lixisenatide (Adlyxin)
Semaglutide (Ozempic)
Sodium-glucose cotransporter-2 inhibitors (SGLT-2i mono and combi)
Canagliflozin (Invokana)
Metformin + Canagliflozin (Invokamet)
Metformin + Canagliflozin extended-release (Invokamet XR)
Dapagliflozin (Farxiga)
Empagliflozin (Jardiance)
Empagliflozin + Linagliptin (Glyxambi)
Metformin + Empagliflozin (Synjardy)
Metformin + Empagliflozin extended-release (Synjardy XR)
Dapagliflozin + Saxagliptin (Qtern)
Metformin + Dapagliflozin extended-release (Xigduo XR)
Ertugliflozin (Steglatro)
Ertugliflozin + Metformin (Segluromet)
Ertugliflozin + Sitagliptin (Steglujan)

1. ATC codes: https://www.whocc no/atc_ddd_index/ at 31 January 2019

ANNEX 5. REVIEWERS AND APPROVAL SIGNATURES

The NIS Protocol must be sent for review to the following individuals **prior to approval**.

Reviewer	**NIS involving BI product(s)**	**NIS not involving BI product(s)**	
		Global NIS	Local NIS
NIS Lead	X	X	X
Global TM Epi	X	X	X
Global TMM / TMMA / TM Market Access	X	X	
Global Project Statistician	X	X	
Global TM RA	X		
Global PVWG Chair	X		
GPV SC	X	X	X
Global CTIS representative	X		
Local Medical Director	X (if local study)		X
Local Head MAcc / HEOR Director	X (if local study)		X
Global TA Head Epi*	X	X	
Global TA Head Clinical Development / Medical Affairs / Market Access*	X	X	
Global TA Head PV RM*	X		
RWE CoE	X	X	
PSTAT / PSTAT-MA (for NISnd only)	X	X	X
NIS DM	X	X	X
Local Head MA/Clinical Development			X (does not apply to NISed without chart abstraction)

* After review by Global TM for function

Study Title: Post-authorization safety study (PASS) to assess the risk of acute pancreatitis in type 2 diabetes mellitus (T2DM) patients newly initiating empagliflozin compared to other oral non-incretin/non-sodium glucose co-transporter-2 inhibitors (SGLT2)-based glucose lowering drugs

Study Number: 1245-0201

Protocol Version: 1.0

I herewith certify that I agree to the content of the study protocol and to all documents referenced in the study protocol.

Position: NIS [redacted]	Name/Date: [redacted]	Signature:
Position: Global TM Epi	Name/Date: [redacted]	Signature:
Position: Global TMM	Name/Date:	Signature:
Position: Global TMMA	Name/Date:	Signature:
Position: Global TM Market Access	Name/Date:	Signature:
Position: Global Project Statistician	Name/Date:	Signature:
Position: Global safety	Name/Date:	Signature:
Position: Global PVWG Chair	Name/Date:	Signature:
Position: Global TM RA	Name/Date:	Signature:
Position: GPV SC	Name/Date:	Signature:
Position: Global CTIS representative	Name/Date:	Signature:
Position: Global TA Head Epi*	Name/Date:	Signature:
Position: Global TA Head Clinical Development / Medical Affairs*	Name/Date:	Signature:

Position: Global TA Head Market Access*	Name/Date: _____	Signature**:** _____
Position: Global TA Head PV RM*	Name/Date: _____	Signature**:** _____
Position: RWE CoE	Name/Date: _____	Signature**:** _____
Position: RWE CoE	Name/Date: _____	Signature**:** _____
Position: RWE CoE	Name/Date: _____	Signature**:** _____
Position: NIS DM	Name/Date: _____	Signature**:** _____

APPROVAL / SIGNATURE PAGE

Document Number: c37704615 **Technical Version Number:1.0**

Document Name: nis-protocol-1245-0201

Title: Post-authorization safety study (PASS) to assess the risk of acute pancreatitis in type 2 diabetes mellitus (T2DM) patients newly initiating empagliflozin compared to other oral non-incretin/non-sodium glucose co-transporter-2 inhibitors (SGLT2)-containing glucose lowering drugs

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-[redacted] Safety Evaluation Therapeutic Area	[redacted]	14 Dec 2021 11:31 CET
Approval-Team Member Medicine		14 Dec 2021 11:44 CET
Approval		14 Dec 2021 13:32 CET
Approval-EU Qualified Person Pharmacovigilance		14 Dec 2021 16:11 CET
Approval		14 Dec 2021 17:46 CET
Approval-On behalf of [redacted] or [redacted] or [redacted]		14 Dec 2021 18:56 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed