Boehringer Ingelheim

STATISTICAL AND EPIDEMIOLOGICAL ANALYSIS PLAN (SEAP) FOR NON-INTERVENTIONAL STUDIES (NIS)

Document Number:	c37922104-02
BI Study Number:	1245-0201
BI Investigational Product(s)	Jardiance® (empagliflozin)
Title:	Statistical and Epidemiological Analysis Plan (SEAP) for 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 agents
Brief lay title:	To assess the risk of acute pancreatitis in patients with type 2 diabetes treated with empagliflozin
SEAP version identifier:	1.0
Date of last version of SEAP:	03 December 2021
NIS Statistician [SEAP author]	[redacted]
NIS [redacted] [SEAP reviewer]	[redacted] Global Epidemiology
NIS Data [redacted] [SEAP reviewer]	[redacted]

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

BI	Boehringer Ingelheim
CI	Confidence Interval
DMRP	Data management and review plan
HDPS	High dimensional propensity score
IHD	Instant Health Data
IQR	Interquartile range
NIS	Non-interventional study
SEAP	Statistical and epidemiological analysis plan
SGLT2i	Sodium glucose co-transporter-2 inhibitor
T2DM	Type 2 diabetes mellitus
US	United States

2. RESPONSIBLE PARTIES

NIS Statistician [SEAP author]:

Name, degree(s)	Title	Affiliation	Address
[redacted]	Global Epidemiologist	[redacted]	
	[redacted]		
	[redacted]		
	[redacted]		

SEAP reviewers are:

- BI NIS [redacted] [SEAP reviewer] (in all cases): [redacted] Global Epidemiology
- NIS Data [redacted] [SEAP reviewer] (in all cases): [redacted] and [redacted]
- [redacted] [SEAP reviewer] (for all globally initiated studies and for local studies) involving BI products and Global NIS not involving BI products: [redacted], and [redacted]
- TSTAT (for NISnd only): Not Applicable
- TM Epi [SEAP reviewer] (When BI NIS [redacted] is not TM Epi; in all cases): [redacted], Global Epidemiology

3. PURPOSE AND SCOPE

SEAP reviewers are expected to be familiar with the NIS protocol entitled "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 agents", version 1.0 dated 29 November 2021 unless otherwise stated.

The SEAP addresses the details of the implementation of this study. In the SEAP, you can find the detailed operational definitions on how to identify each of the index medication cohorts, detailed data analysis plan such as the propensity score matching, meta-analysis, and Main analysis plan. In addition, the study covariates are captured in the Annex 3.

4. AMENDMENTS AND UPDATES

None.

5. RESEARCH QUESTION AND OBJECTIVE

This non-interventional cohort study using data from two large United States claims databases will describe the risk of acute pancreatitis among patients with type 2 diabetes mellitus (T2DM) 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 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).

6. RESEARCH METHODS

6.1 STUDY DESIGN

Please see the study protocol.

6.2 SETTING

Please see the study protocol.

6.2.1 Study period

The patient selection period will be from 01 August 2014 to the latest data-cut available in Marketscan (30 September 2020) and Optum (31 March 2021). Patients will be selected into the study at any time during this period once they fulfil the study eligibility criteria.

6.2.2 Baseline period (lookback period)

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 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-based glucose lowering agents without use of these medications in the prior 6 months) and describe baseline parameters, such as prior medical history and medications.

6.2.3 Follow up

Follow up starts at the day after the index date until the first qualifying event has been met (see table 2 and 3 of the study protocol).

6.3 STUDY POPULATION

Please see the study protocol for the details.

Codes to select study population are listed in Annex 1.

One of the risk factors of acute pancreatitis is severity of diabetes and diabetes duration [R10-6620, R10-2088]. In the Optum and Marcketscan databases duration of diabetes can not be measured for all patients, therefore chronic use of insulin at baseline was selected as an exclusion criterion to remove severe cases of diabetes who are already at higher risk of developing acute pancreatitis. We defined 60 (or more) days of continuous exposure as chronic use of insulin for the exclusion criteria.

The operational steps are as follows:

Insulin prescriptions will be extracted during the 6 months baseline period according to insulin medication codes listed in Annex 2. Despite the variations in package size and dosing schedule, a majority of insulin prescriptions are dispensed with 30 days' supply [R21-4257, R21-4258].

The continuous exposure episode of insulin is constructed by linking insulin prescriptions with allowed less or equal 30 gap days [R21-0580]. If any of continuous exposure episodes have 60 or more than 60 days duration, this will be considered as chronic use of insulin and this patient will be excluded from the cohort.

6.4 STUDY VISITS

Not applicable.

7. VARIABLES

Study variables are explained the study protocol section 9.3. you can find attritional operational definitions below:

7.1 EXPOSURES

Please check section 9.3.1 of the study protocol.

7.1.1 Operational definitions on how to identify each of the index medication cohorts:

For index medication determination, we first select all patients with any of Empagliflozin, TZD, SU and Metformin prescriptions within study period. Then we evaluate index drug for each patient following this order: Empagliflozin → TZD → SU → Metformin. Therefore, each patient will be classified into one of index cohorts only once. The details for Empagliflozin initiators are provided below and all other drugs follow the same approach.

Empagliflozin initiators:
1. Between Aug 2014 and latest data cut we will choose all Empagliflozin new users. The date of first Empagliflozin prescription will be selected as index date. New users should not have any prescriptions for Empagliflozin in 6 months prior to the index date.
2. In the next step we will check which of the Empagliflozin initiators use metformin, or SU in the 6-month baseline period

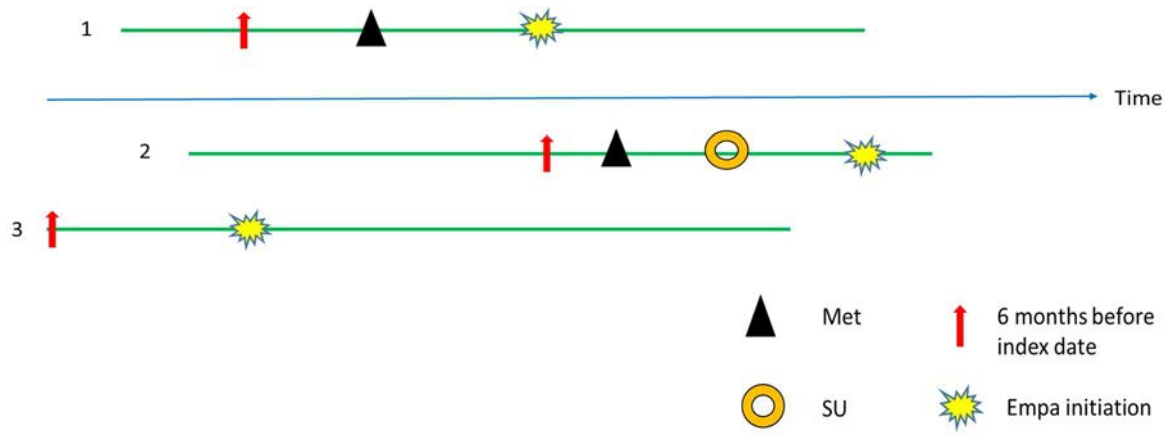


Figure 1 Diagram for Mono, Combo or Triple groups creations

Code list for exposure variables is available in Annex 2.

The index date in both groups will be the date of prescription of empagliflozin or other hypoglycaemic therapies (index medication), and the planned study follow-up period starts at the day after index date.

7.1.2 Definition of continuous exposure, discontinuation, switch or add-on

The continuous exposure periods of index drug have been created by linking all prescriptions with days of supply with 30 days grace period in between. Note: 30 days grace period is used in main analysis. 90 days grace period will be used in sensitivity analysis. The discontinuation is when there is more than 30 days gap from current prescription exposure end to next prescription date. The discontinuation date is 30 days after the end of days of supply of the last prescription date.

Addition of a new medication means when the prescription date of this new medication is before the last prescription date of the index continuous exposure. The prescription date of new medication is add-on date.

Switch to new medication means the prescription date of this new medication is on or after the last prescription date of the index continuous exposure and before the end of discontinuation. The prescription date of new medication is switch date. Different scenarios for switch, discontinue, or add on were mentioned in the study protocol.

7.1.3 Definition the censored follow-up end

The study will be conducted utilizing a modified "as-treated" approach. The follow up time starts from index date till the earliest date of these following events:

1. Discontinuation of index drug.
2. Switch or add-on the within treatment line comparator (other SGLT2 in empagliflozin group or the comparator group. Please refer to Table 1 for different switch or add-on scenarios for each group.
3. Outcome: AP event. The first date of AP event is the event date.
4. The minimum date of death date or enrollment end date or study end date

As long as it is not the treatment line comparator, patients are allowed to add a non-incretin/non-SGLT2i hypoglycemic agent to their index therapy and can also switch to non-incretin/non-SGLT2i hypoglycemic agents.

Based on the feasibility studies, the patients having fixed dose of Empagliflozin + Metformin are definied as dual Empagliflozin patients. The index date is the first prescription of fixed dose prescription.

For the patients starting Metformin then Empagliflozin, these patients are free dose Empagliflozin + Metformin dual patients and they are definied as dual Empagliflozin patients by following exposure group definition process. The index date is the first Empagliflozin prescription date.

For both situations, the index drug is Empagliflozin. The cencor date will be captured by following the same rule.

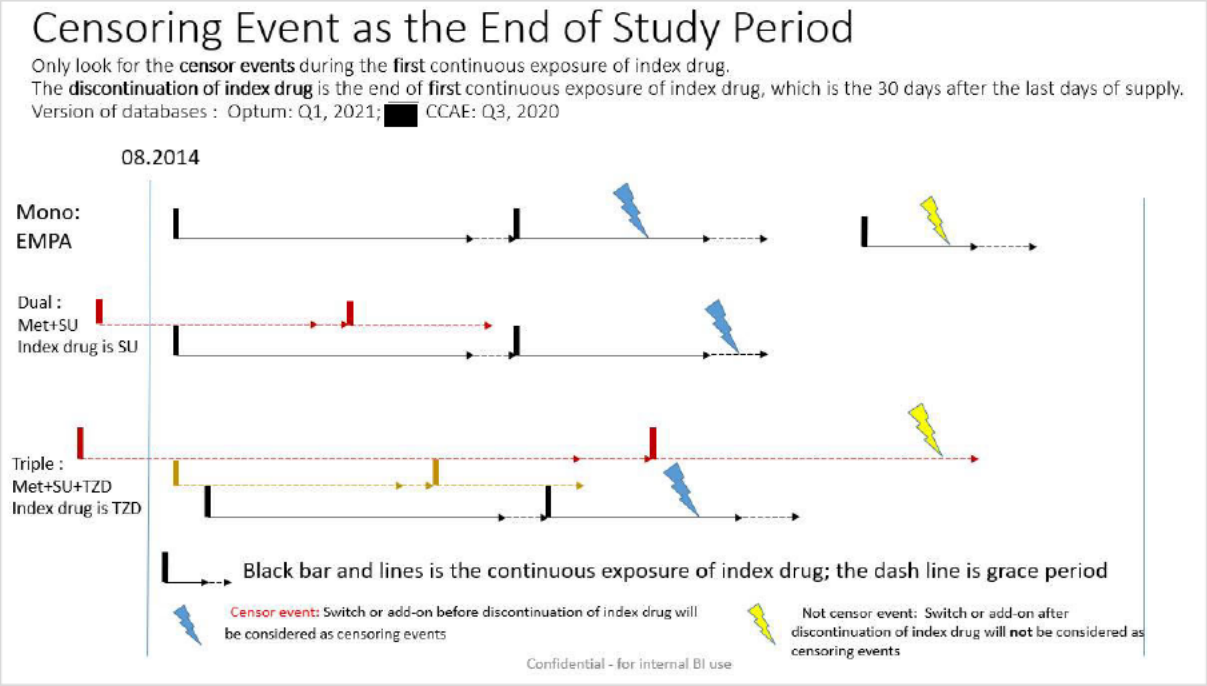


Figure 2 Diagram for definition of the censored end of follow up

7.2 OUTCOMES

Please check section 9.3.2. of the study protocol.

7.3 COVARIATES

Please check section 9.3.3. of the study protocol. List of covariates and operational definitions are added to Annex 3.

8. DATA SOURCES

Please check section 9.4 of the study protocol.

9. DATA MANAGEMENT AND SOFTWARE/TOOLS

Data 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. All study details are addressed either in the protocol, SEAP, or DMRP.

9.1 SOFTWARE/TOOLS

The cohort selection part will be conducted in IHD platform and the data analysis will be run in BI internal server using SAS software 9.4 ([redacted]) or R Studio 3.5.2.

9.2 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.

9.3 HANDLING OF INCONSISTENCIES IN DATA AND OUTLIERS

For lab values, distribution of each variable will be assessed. The extreme outliers will be treated as missing values approaches to handling missing values are described in the previous section.

10. DATA ANALYSIS

10.1 DEFINITIONS

Please check the study protocol section 9.7.1.

10.2 PROPENSITY SCORE

Please check study protocol section 9.7.2.

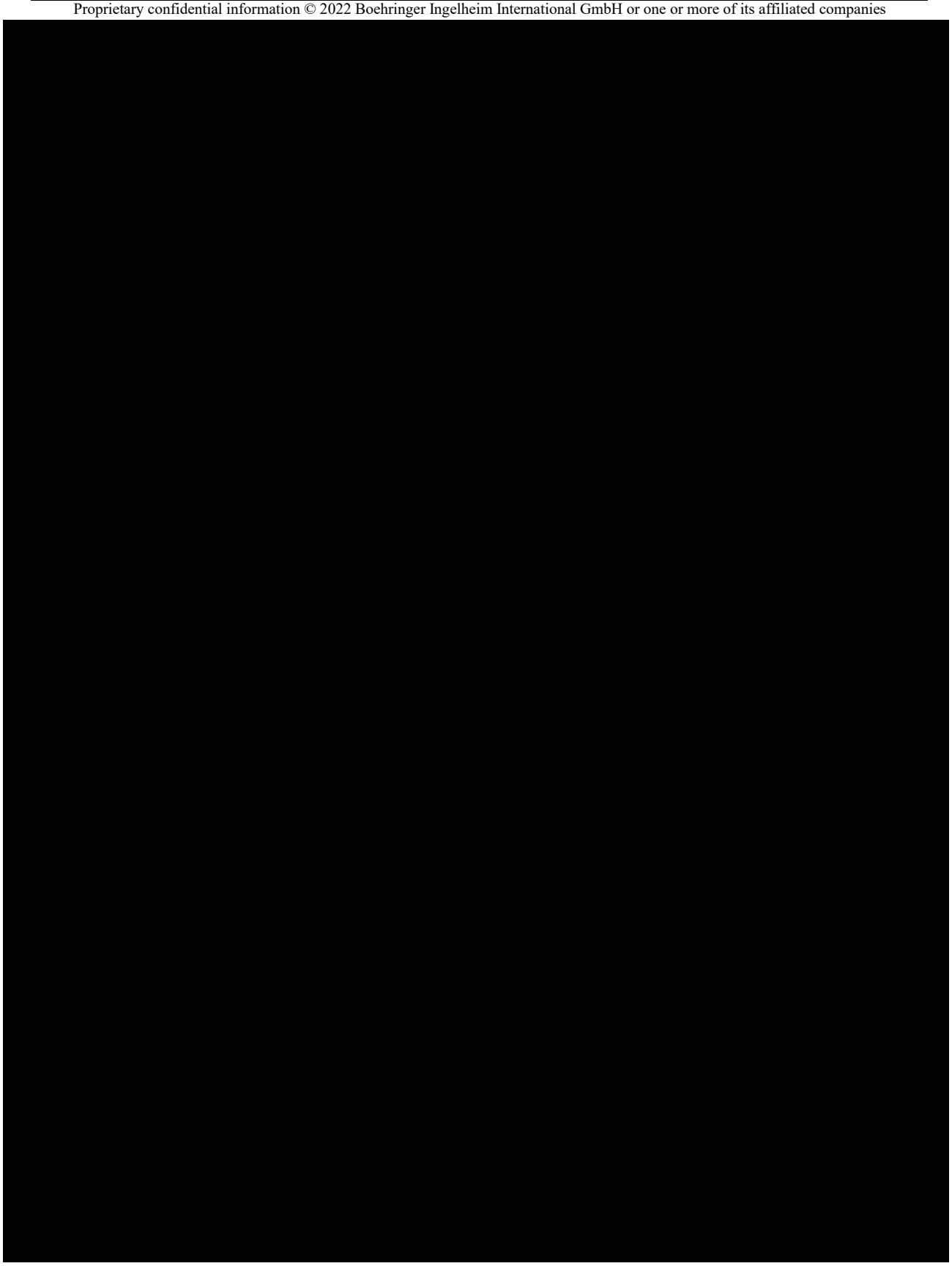
10.3 MAIN ANALYSIS

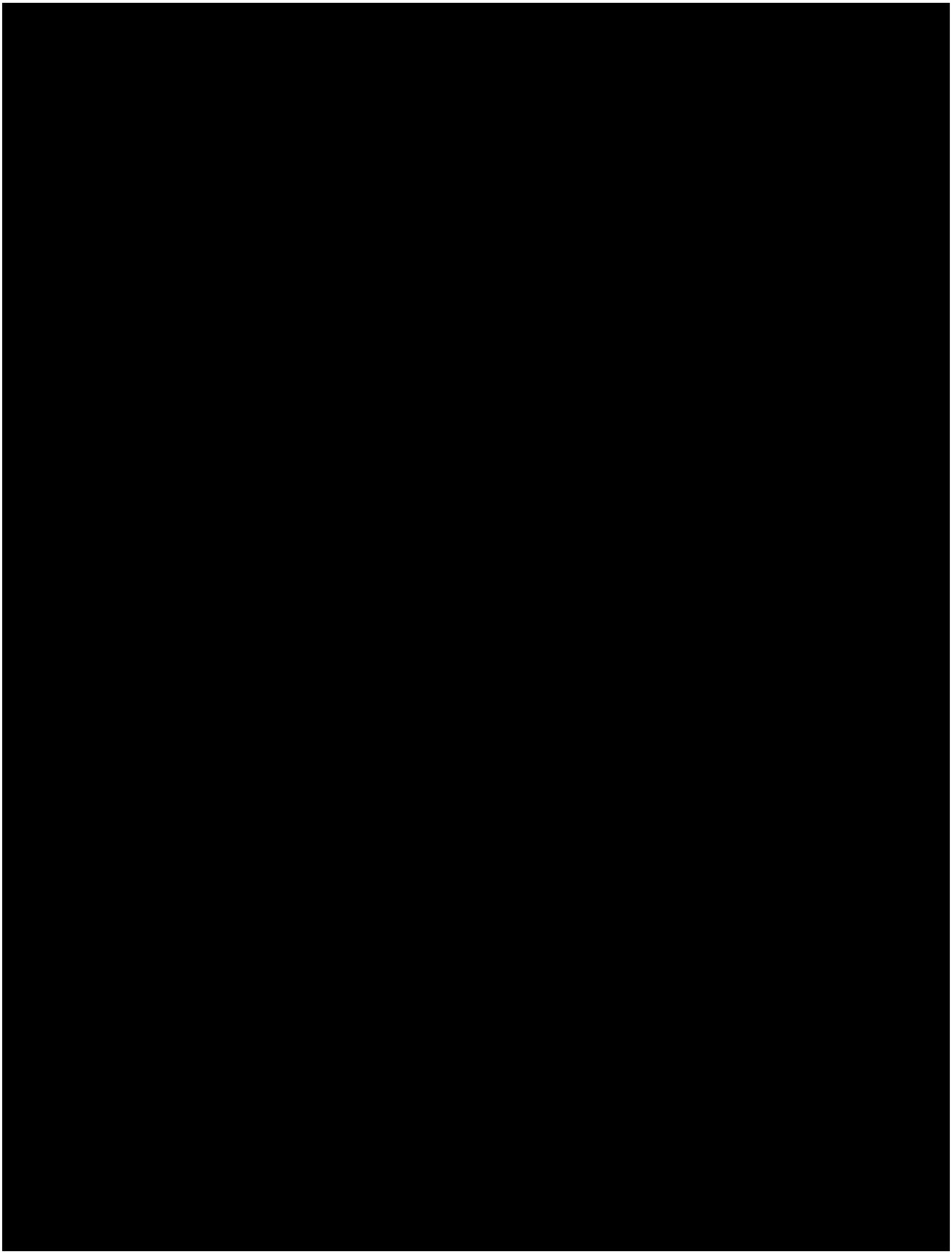
Please check study protocol section 9.7.3.

10.4 META-ANALYSIS

Please check study protocol section 9.7.4.

[redacted]





10.6 SENSITIVITY ANALYSIS

See relevant section of the study protocol.

10.7 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.

11. 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 has been 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.

12. REFERENCES

12.1 PUBLISHED REFERENCES

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.
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.
R20-3573	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
R13-0525	Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology 2009 ; 20(4) ; 512-522.
R13-2767	Rassen JA, Glynn RJ, Brookhart MA, Schneeweiss S. Covariate selection in high-dimensional propensity score analyses of treatment effects in small samples. Am J Epidemiol 2011 ; 173(12) ; 1404-1413.
R21-0580	Hadjiyianni I, Desai U, Suzuki S, Ivanova JI, Cao D, Kirson NY, et al. Basal insulin persistence, associated factors, and outcomes after treatment initiation: a retrospective database study among people with type 2 diabetes mellitus in Japan. Diabetes Ther 2017 ; 8; 149-166.
R21-4257	Buysman E, Conner C, Aagren M, Bouchard J, Liu F. Adherence and persistence to a regimen of basal insulin in a pre-filled pen compared to vial/syringe in insulin-naive patients with type 2 diabetes. DOI: 10.1185/03007995.2011.598500. Curr Med Res Opin 2011 ; 27(9) ; 1709-1717.
R21-4258	Eby EL, Bajpai S, Faries DE, Haynes VS, Lage MJ. The association between adherence to insulin therapy and health care costs for adults with type 2 diabetes: evidence from a U.S. retrospective claims database. DOI: 10.18553/jmcp.2020.26.9.1081. J Managed Care Spec Pharm 2020 ; 26(9) ; 1081-1089.
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. Diabetes Obes Metab 2010 ; 12(9) ; 766-771.
R10-2088	Noel RA, Braun DK, Patterson RE, Bloomgren G. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a

	retrospective cohort study. Diabetes Care 2009 ; 32(5) ; 834-838.
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.
R20-1531	Anand ER, Major C, Pickering O, Nelson M. Acute pancreatitis in a COVID-19 patient. DOI: 10.1002/bjs.11657. 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. DOI: 10.1016/j.pan.2020.04.021. Pancreatology, Article in Press, Corrected Proof, Available online 5 May 2020, doi: 10.1016/j.pan.2020.04.021; 2020. p. 665-667.
R20-1536	Wang F, Wang H, Fan J, Zhang Y, Wang H, Zhao Q. Pancreatic injury patterns in patients with COVID-19 pneumonia. DOI: 10.1053/ Gastroenterology, Journal Pre-proof, Published online: April 01, 2020, doi: 10.1053/ j.gastro.2020.03.055; 2020. p. 367-370.
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. doi: 10.1101/2020.02.28.20029181; 2020.
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? Source: 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.
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 ; 43(11) ; 1130-1139.

12.2 UNPUBLISHED REFERENCES

Not applicable.

ANNEX 1. 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 2. MEDICATION CODES 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)
Insulin

ANNEX 3. STUDY COVARIATES

N	Category	Variables	Definition
1	Demographics	Age	- By year - By category (18-54, 55-64, 65-74, 75+)
		Gender	- Male, Female
		Smoking	All codes could be found in the following excel file:  1245-0201%20codes%20part%201_03022
		Alcohol abuse or dependence	
		Drug abuse or dependence	
		Overweight	
		Obesity	
		Calendar quarter of cohort entry	
		Calendar year of cohort entry	
2	Comorbidity indexes	Elixhauser comorbidity index	- R14-4775
		Charlson comorbidity index	
3	Diabetes specific complications	Diabetes retinal problems	- Diabetic retinopathy, diabetes with other ophthalmic manifestations, Retinal detachment, vitreous hemorrhage, vitrectomy, retinal laser coagulation therapy. Codes presented in the following excel file:  1245-0201%20codes%20part%201_03022
		Diabetic neuropathy	
		Diabetic nephropathy	
		Hypoglycaemia	
		Hyperglycaemia	
		Disorders of fluid electrolyte and acid-base balance	
		Diabetic ketoacidosis	
		Hyperosmolar hyperglycemic nonketotic syndrome (HONK)	
		Diabetes with peripheral circulatory disorders	
		Diabetic foot	
		Gangrene	
		Lower extremity amputation (lower extremity amputation diagnosis code, lower extremity amputation procedure code (ICD), lower extremity amputation procedure code (CPT).)	
		Osteomyelitis	
		Skin infections	
		Erectile dysfunction	
		Diabetes with unspecified complication	
		Diabetes mellitus without mention of complications	

4	General medical history	Hypertension	- Codes presented in the following excel file: 1245-0201%20codes%20part%202_03022 1245-0201%20Codes%20part%203_0304. 1245-0201%20codes%20part%205_04162
		Hyperlipidaemia	
		Myocardial infarction (Acute MI and old MI)	
		Angina (ACS/unstable angina, stable angina)	
		Coronary atherosclerosis and other forms of chronic ischemic heart disease	
		Cardiac procedures (Previous cardiac procedure (CABG or PTCA or Stent))	
		Ischemic stroke (w and w/o mention of cerebral infarction)	
		Hemorrhagic stroke	
		TIA	
		Cerebrovascular disease (Other cerebrovascular disease, late effects of cerebrovascular disease, Cerebrovascular procedure)	
		Heart failure (CHF)	
		Peripheral Vascular disease or PVD surgery	
		Atrial fibrillation	
		Other cardiac dysrhythmia	
		Cardiac conduction disorders	
		Other CVD	
		COPD	
		Asthma	
		Obstructive sleep apnoea	
		Renal	
		Osteoarthritis	
		Rheumatoid arthritis	
		Dorsopathies	
		Fractures	
		Falls	
		Osteoporosis	
		Hypothyroidism	
		Hyperthyroidism	
		Other disorders of thyroid gland	
		Depression	
		Anxiety	
		Sleep disorders	
		Neoplasms	

		Human immunodeficiency virus infection	
		Ulcerative colitis	
		Crohn's disease	
		Gastroesophageal reflux disease	
		Gastrointestinal haemorrhage	
5	Use of insulin		
6	Use of other oral hypoglycaemic agents		
7	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	
8	Use of any other medications not mentioned above	• Agents acting on the renin-angiotensin system • Antibacterials for systemic use • Antidepressants	

		• Antiepileptics • Antiinflammatory and antirheumatic products • Antineoplastic agents • Antipsoriatics • Antithrombotic agents • Beta-blocking agents • Calcium channel blockers • Diuretics • Drugs for acid-related disorders • Drugs for obstructive airway diseases • Immunosuppressants • Lipid-modifying agents • Opioids • Psycholeptics • Psychostimulants, agents used for ADHD, and nootropics	
9	History of acute pancreatitis risk factors	• Abdominal surgery • Alcoholism • Cystic fibrosis • Gallstones and other gallbladder and biliary tract disorders • High calcium levels in the blood (hypercalcemia) • Hyperparathyroidism • Hypertriglyceridemia • Infection • Injury to the abdomen • Lupus • Liver disease • Pancreatic disease	Codes are listed in the following excel file:  1245-0201%20Codes%20part%204%20-%
10	Lab test results (when available)	• 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),	

		carbamid (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 120min [add reference]. • HbA1c (%) • LDL level (mg/dl) • HDL level (mg/dl) • Total cholesterol (mg/dl) • Triglyceride level (mg/dl) • Creatinine (mg/dl) • BUN (mg/dl) • BNP • NT-proBNP • Lipase	
11	Procedures	• Abdominal ultrasound	

ANNEX 4. REVIEWERS AND APPROVAL SIGNATURES

The NIS SEAP 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
NIS Data Manager	X	X	X
TSTAT (for NISnd only)	X	X	X
RWE CoE	X	X	

* When BI NIS lead is not TM Epi

Study Title: Statistical and Epidemiological Analysis Plan (SEAP) for 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 hypoglycemic agents – Version 1.0

Study Number: 1245-0201

Protocol Version: Version 1.0

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

Position: NIS [redacted]	Name/Date: [redacted] / 23 Jul 2021	Signature: _____
Position: TM BDS	Name/Date: [redacted] / dd mmm yyyy>	Signature: _____
Position: Global TM Epi	Name/Date: [redacted] ddmmmyyyy	Signature: _____
Position: NIS Data [redacted]	Name/Date: [redacted] _____	Signature: _____
Position: _____	Name/Date: _____	Signature: _____