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Subject: GLP-1 agonist, DPP-4 inhibitors, acute pancreatitis

Author(s): PPD

Indication Studied: Type II Diabetes Mellitus

PASS INFORMATION

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Research question and objectives	The objectives of this study are: 1. To evaluate the association between albiglutide and acute pancreatitis as compared to the association observed between this outcome and use of other antidiabetic agents (ADAs) (excluding GLP-1 agonists and DPP-4 inhibitors). 2. To evaluate the association between GLP-1 agonists (including and excluding albiglutide), DPP-4 inhibitors and acute pancreatitis as compared to the association observed between this outcome and use of other ADAs.
Country(-ies) of study	Retrospective observational analysis conducted in a U.S. medical and pharmacy claims database, Truven Marketscan Commercial.

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I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of the study PRJ2335.

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1. LIST OF ABBREVIATIONS

ADA	AntiDiabetic Agent
AE	Adverse Event
CCI	Charlson Comorbidity Index
CI	Confident Interval
COBRA	Consolidated Omnibus Budget Reconciliation Act
DDP-4	DipeptiDyl Peptidase 4
ERCP	Endoscopic Retrograde CholangioPancreatography
FDA	Food and Drug Administration
GLP-1	Glucagon-Like Peptide-1
GSK	GlaxoSmithKline
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio
ICD-9	International Classification of Diseases-version 9
PASS	Post-Authorisation Safety Study
PhD	Doctor of Philosophy
PID	Project Information Document
PRAC	Pharmacovigilance Risk Assessment Committee
PBRER	Periodic Benefit Risk Evaluation Report
QC	Quality Check
RR	Risk Ratio
SAS	Statistical Analysis Software
SD	Standard Deviation
SOP	Standard Operating Procedure
T2D	Type 2 diabetes
US	United States

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None

2. RESPONSIBLE PARTIES

N/A

INVESTIGATORS

N/A

STUDY ADVISORY COMMITTEE

N/A

3. ABSTRACT

Title

Observational Study of the Risk of Acute Pancreatitis in Subjects Exposed to Albiglutide, Other GLP-1 Agonists or DPP-4 Inhibitors Compared to Other Antidiabetic Agents

Keywords

GLP-1 agonist, DPP-4 inhibitors, acute pancreatitis

Rationale and background

The role of GLP-1 agonists in type 2 diabetes (T2D) treatment is still evolving and several GLP-1 agonists have recently been newly marketed (e.g., albiglutide, lixisenatide and dulaglutide) or are in the pipeline (e.g., semaglutide). There have been some safety concerns raised about the risk of acute pancreatitis due to the use of GLP-1 agonists and DPP-4 inhibitor therapies, particularly with their long-term use, which may initiate histological changes leading to chronic pancreatitis and, potentially, pancreatic cancer. This study is part of the Risk Management Plan for albiglutide and addresses the safety question about the risk of acute pancreatitis for the incretin mimetic class of antidiabetic agents in general and for albiglutide in particular.

This interim report provides an early assessment of the pancreatitis risk of the first 5,000 subjects treated with albiglutide accrued on the database since launch.

Research questions and objectives

The objectives of this study are:

1. To evaluate the association between albiglutide and acute pancreatitis as compared to the association observed between this outcome and use of other ADAs (excluding GLP-1 agonists and DPP-4 inhibitors).
2. To evaluate the association between GLP-1 agonists (including and excluding albiglutide), DPP-4 inhibitors and acute pancreatitis as compared to the association observed between this outcome and use of other ADAs.

Study design

The study design was a retrospective cohort study conducted in the Truven Marketscan Commercial (formerly, Thomson Reuters) health insurance database. As stipulated in the study protocol, this interim analysis was conducted at the point where a minimum of N=5,000 subjects exposed to the newly marketed GLP-1 agonist albiglutide had accrued on the database.

Population

The study population consisted of subjects aged ≥ 18 and ≤ 64 years, who were continuously enrolled in the health plan for ≥6 months, had at least one claim of T2D diagnosis during the study period and who had at least two consecutive prescription claims for a new ADA (ingredient) from 2014 (when albiglutide was launched in the U.S.) till the end of the study period. The date of first prescription for the new ADA in the study period was defined as the 'index date' and the drug was referred to as the 'index ADA'. Subjects were followed from the index date until the first occurrence of acute pancreatitis, loss of pharmacy benefits, disenrollment from the database, turning 65 years old, discontinuation of the index medication, switching of the study medication groups, or end of follow-up in the database, whichever came earlier.

Variables and data sources

Outcome Definitions: Acute pancreatitis in the study groups was identified in the post-index follow up period by hospitalization claims containing ICD-9 code 577.0 (acute pancreatitis) as a primary discharge diagnosis and the corresponding ICD-10 codes.

Exposure Definitions: Five exposure groups were created based on the ADA prescription they received at the index date.

1. albiglutide
2. GLP-1 agonist excluding albiglutide
3. GLP-1 agonists including albiglutide
4. DPP-4 inhibitors
5. Other ADAs

Data sources: The study was conducted using the Truven Marketscan Commercial database which is one of the largest claims databases in the U.S., linking paid claims and encounter data to detailed patient information across sites and types of providers, and over time.

Interim Results

This interim report provides results of the study objectives assessing if there are any early findings on the risk of acute pancreatitis associated with the drug.

In proportional hazard models adjusted for key co-variables, the risk of pancreatitis comparing albiglutide to other ADA was not elevated [0.86 (0.27, 2.73)], nor was pancreatitis risk comparing GLP-1 with and without albiglutide to other ADA [0.91(0.63, 1.33); 0.92 (0.62, 1.35) respectively] and DPP-4 compared to other ADA [0.90 (0.65, 1.24)].

Conclusions

In summary, the results of our study suggest that, compared with use of any other ADAs, the use of albiglutide in particular, and the incretin based drugs in general, is not associated with an increased risk of acute pancreatitis among subjects with T2D.

4. AMENDMENTS AND UPDATES

No further amendments were made to the protocol (GSK Document number 2014N211972_00) as a result of the analyses conducted to produce this interim study report.

The recruitment of subjects into future albiglutide studies will be limited by the planned withdrawal of albiglutide from global markets in July 2018. Consequently, study sample size will be too small to provide sufficient power to detect smaller clinically important relative risks. For this reason, GSK has proposed in the Type II variations assessment report (EMA/756852/2016) to terminate the final and conclusive part of this study, which was specified to be completed when albiglutide counts reach 31,000 subjects.

5. MILESTONES

Milestone	Planned date
Submission of study protocol to PRAC	September 2014
Submission of updated protocol to PRAC	February 2015
Submission of updated protocol to PRAC	June 2015
Provide counts of albiglutide subjects in Truven Marketscan Commercial database	Yearly starting in May 2016 as part of PASS Progress Report with the PBRER.
Start of data analysis	Contingent on albiglutide counts reaching 5,000; potentially 2016; actual start of analysis: 15th May 2017
Submission of preliminary analysis to PRAC	(6 months post start of data analysis) Actual submission with next PBRER in May 2018 as agreed with PRAC
Final report of study results when albiglutide counts reach 31,000 subjects	(9 months post start of data analysis) We requested to terminate this part as this number of subjects exposed will not be achievable with the withdrawal of albiglutide from the market

6. RATIONALE AND BACKGROUND

6.1. Background

Albiglutide (GSK716155) is a novel, long-acting GLP-1 receptor agonist generated through genetic fusion of 2 modified human glucagon-like peptide-1 (GLP-1) molecules linked in tandem to the amino terminus of human albumin. As an analogue of GLP-1 (97% homology for the GLP-1 moiety), albiglutide was designed to retain the therapeutic actions of endogenous GLP-1 while having a greatly extended duration of action. It retains the glucose-dependent insulinotropic activities of GLP-1 in vitro and in vivo. As an agonist at the GLP-1 receptor, albiglutide acts on pancreatic β-cells to augment glucose-dependent insulin secretion and consequently improve glycaemia.

Market authorization of albiglutide in Europe was granted on 21 March 2014 and in the US on 15 April 2014.

There have been some safety concerns raised about the risk of acute pancreatitis due to use of GLP-1 agonists and DPP-4 inhibitor therapies, particularly with their long-term use, which may initiate histological changes leading to chronic pancreatitis and, potentially, pancreatic cancer (Nauck, 2013). Post-marketing cases of pancreatitis were reported in subjects taking exenatide, leading to an added label warning of risk of acute pancreatitis for exenatide (FDA, 2008). In clinical trials, acute pancreatitis was reported more often among patients taking liraglutide, leading the FDA to require risk evaluation and mitigation strategy for liraglutide (Parks, 2010).

During the Phase III program for albiglutide, the incidence of acute pancreatitis (adjudicated as likely to be related to therapy) in the clinical studies was 0.3% for

albiglutide compared to 0% for placebo and 0.1% for comparators (i.e. liraglutide, pioglitazone, glimepiride, sitagliptin, and insulin glargine) with or without additional background antidiabetic therapy (e.g. metformin).

Nine observational studies examining the risk of acute pancreatitis with GLP-1 receptor agonists and DPP-4 inhibitors have been published. Results from seven of these studies do not support the hypothesis that acute pancreatitis risk is increased with incretin-based therapy use. No association was found between acute pancreatitis and incretin-based therapies in five studies utilizing insurance claims databases (Garg, 2010, Dore, 2009, Romley, 2012, Wenten, 2012, and Funch, 2013) or in one study using medical records (Li, 2013) in the US. Increased risk was reported among past users (use more than 62 days prior to event) in a cohort analysis by Dore et al., but this result was not confirmed by a nested case-control analysis of the same population, and the authors concluded there was no evidence of an association (Dore, 2011). An increased risk of acute pancreatitis in relation to GLP-1 receptor agonists was reported in two studies (Dore, 2013, Singh, 2013). In a pooled analysis of two insurance claims databases, Dore et al. found a 30-60% increased risk of acute pancreatitis with exenatide use, either current (time during current medication-days supply plus 31 days) or past use (time following 62 days after discontinuing current treatment) (Dore, 2013). Incidence of acute pancreatitis was 129.8 per 10,000 patient years (PY) with current exenatide use and 158.3 with past use, compared to 95.0 with use of other antihyperglycemic medications. It is not possible to estimate the time to acute pancreatitis from this study as a time to event analysis or Kaplan-Meier curves were not provided by the authors. In a population-based matched case-control study, Singh et al. reported a doubling of the odds for hospitalization for acute pancreatitis among current (within 30 days of acute pancreatitis), recent (30 days to 2 years), or any exenatide or sitagliptin use, in which 55, 72, and 87 cases were reported, respectively, from a total of 1,269 cases among type 2 diabetics (Singh, 2013).

We also reviewed the literature for the duration from exposure to GLP-1 receptor agonists to the diagnosis of acute pancreatitis. Pooled data from Novo Nordisk–sponsored phase 2 and 3 trials with liraglutide completed by 19 April 2013 included 6,345 subjects exposed to liraglutide with a total exposure of 5,021 patient-years. Eight cases of acute pancreatitis were found. The latency period for the development of acute pancreatitis among the eight liraglutide cases ranged from 49 days to 668 days with a mean of 279 days and a median of 264 days. In six of these eight cases, the onset of acute pancreatitis occurred >6 months after liraglutide initiation (Jensen, 2015). In the 7 Phase III albiglutide studies without routine on-therapy amylase and lipase assessments, the Pancreatitis Adjudication Committee adjudicated six cases of probable or definite pancreatitis and at least possibly related to albiglutide. The time of onset was relatively late in the trial (range: Days 153 to 874).

Since the role of GLP-1 agonists in T2D treatment is still evolving and several GLP-1 agonists are newly marketed (e.g. albiglutide, lixisenatide and dulaglutide) or in the pipeline (e.g., semaglutide), it is important to understand the risk of acute pancreatitis with the currently marketed GLP-1 agonists.

6.2. Rationale

This study is part of the risk management plan for albiglutide and addresses the safety question about the risk of acute pancreatitis for the incretin mimetic class of antidiabetic agents in a real-world setting. The study provides the incidence rate of acute pancreatitis with albiglutide as well as other GLP-1 receptor agonist and DPP-4 inhibitors (collectively referred to as incretin mimetics). It provides relative risks of acute pancreatitis with albiglutide compared to other antidiabetic agents (ADAs) as well as other GLP-1 receptor agonists and DPP-4 inhibitors compared to other ADAs.

This interim report provides results of the study objectives assessing the first 5,000 subjects on albiglutide accrued on the database, which was conducted to determine if there were any early findings on an increased risk of acute pancreatitis associated with albiglutide.

7. RESEARCH QUESTION AND OBJECTIVES

The objectives of this study are:

1. To evaluate the association between albiglutide and acute pancreatitis as compared to the association observed between this outcome and use of other ADAs (excluding GLP-1 agonists and DPP-4 inhibitors).
2. To evaluate the association between GLP-1 agonists (including and excluding albiglutide), DPP-4 inhibitors and acute pancreatitis as compared to the association observed between this outcome and use of other ADAs.

8. RESEARCH METHODS

8.1. Study design

The study design was a retrospective cohort study using the Truven Marketscan Commercial (formerly, Thomson Reuters) health insurance database. As stipulated in the study protocol, this interim analysis was conducted, becausea number of more than N=5,000 albiglutide users had accrued on the database.

8.2. Study Population and Setting

The study was conducted using the Truven Marketscan Commercial database, which is one of the largest claims databases in the U.S.

The study population consisted of subjects aged ≥ 18 and ≤ 64 years, who were continuously enrolled in the health plan for ≥6 months, had at least 1 claim of T2D diagnosis during the study period and who had at least two consecutive prescription claims for a new ADA (ingredient) from 15th April 2014 (when albiglutide was launched in the U.S.) till the end of the study period (30th September 2016). Subjects having diagnosis of T2D were identified using ICD-9 codes 250.xx (excluding 250.x1 and/or 250.x3 – Type 1 diabetes and 648.0x – gestational diabetes) and the corresponding ICD-

10 codes. The date of first prescription for the new ADA in the study period was defined as the 'index date' and the drug was referred to as the 'index ADA'.

Subjects having evidence of pancreatic disease in the pre-index period (6 months before the index date) were excluded.

8.2.1. Exposure definitions

The study population was classified as albiglutide user, GLP-1 agonist excluding albiglutide user, DPP-4 inhibitor user or other ADA user based on the ADA prescription they receive at the index date.

The GLP-1 agonists included in this study were: exenatide, liraglutide, albiglutide and dulaglutide. The DPP-4 inhibitors included in this study were: sitagliptin, saxagliptin, linagliptin, alogliptin, combinations of sitagliptin and metformin, combinations of sitagliptin and simvastatin, combinations of saxagliptin and metformin, combinations of linagliptin and empagliflozin, combinations of linagliptin and metformin, combinations of alogliptin and metformin, combinations of alogliptin and pioglitazone. The 'other ADA' included in this study were: insulins, biguanides, thiazolidinediones, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, injectable amylin analogues and glycosuric drugs.

A subject could contribute to more than one exposure category as long as s/he qualified as new user of that ADA ingredient, defined as having no evidence of prescription claim(s) for that ADA ingredient in the previous 6 months.

Five study groups were created:

1. albiglutide
2. GLP-1 agonist excluding albiglutide
3. GLP-1 agonists including albiglutide
4. DPP-4 inhibitors
5. Other ADAs

When subjects switched study medication groups, their follow-up was censored for the study medication group to which they had been contributing exposure data. However, if they became "new users" of another study medication group, then they contributed exposure data to the new medication group until they switched again or discontinued. This approach was selected because diabetes is a progressive disease and subjects can be exposed to various antidiabetic medications over the course of their disease. The intent is to capture the various medication exposure categories over time and to attribute the outcome to the appropriate exposure category at the time when the outcome occurs, thus accurately capturing exposure-outcome associations in the study.

Of note is that while subjects could contribute to various study exposure groups during the follow-up period, each study group was assessed individually by comparing each separately against the "other ADA" group (see Section 8.6 Data Analysis).

The exposure data were based on prescription claims for the various antidiabetic agents. Electronic pharmacy dispensing records are considered accurate because pharmacists fill prescriptions with little room for interpretation and are reimbursed by insurers on the basis of detailed, complete, and accurate claims submitted electronically (Levy, 2003; McKenzie, 2000). Accuracy is improved in many systems by software that assigns the corresponding drug codes after automatically comparing the spelling and strength with electronic lists of marketed drugs. Therefore, pharmacy dispensing information is usually seen as the gold standard of drug exposure information compared with self-reported information (West, 1995) or prescribing records in outpatient medical records (West, 1994).

8.2.2. Outcome definitions

Acute pancreatitis in the study groups was identified in the post-index follow up period by hospitalization claims containing ICD-9 code 577.0 (acute pancreatitis) as a primary discharge diagnosis and the corresponding ICD-10 codes.

This ICD-9 code for acute pancreatitis has been validated in an observational study by Moores (Moores, 2012), with a positive predictive value of 60%–80% and a negative predictive value usually greater than 90% using medical chart review results as the gold standard. In our study, the outcome of interest is identified from administrative claims only without independent validation of the data using medical charts. However, claim entries are fully adjudicated by the payer, and any data that appear to be erroneous (i.e., claims with costs that exceed reasonable limits) are excluded on an individual basis.

8.2.3. Confounders and effect modifiers

Information on the following confounders was collected from the 6-month pre-index period:

- subject's demographic information (age as of index date, sex, region)
- pre-existing comorbidities (hypertension, ischemic heart disease, congestive heart failure, myocardial infarction, cerebrovascular disease, cardiac dysrhythmias, hyperlipidemia, overweight and obesity, hypercalcemia, hyperparathyroidism, alcohol dependence syndrome, gall bladder disease, primary and secondary hypertension, and chronic liver disease)
- comorbidity burden calculated as Charlson comorbidity index (CCI) (Deyo, 1992, Quan, 2005). This CCI included the following diseases and scores:

  "Myocardial infarction" (score=1);
  "Congestive heart failure" (score=1);
  "Peripheral vascular disease" (score=1);

"Cerebrovascular disease" (score=1);
"Dementia" (score=1);
"Chronic pulmonary disease" (score=1);
"Rheumatic disease" (score=1);
"Peptic ulcer disease" (score=1);
"Mild liver disease" (score=1);
"Diabetes without chronic complication" (score=1);
"Diabetes with chronic complication" (score=2);
"Hemiplegia or paraplegia" (score=2);
"Renal disease" (score=2);
"Any malignancy" (score=3);
"Moderate or severe liver disease" (score=6);
"Metastatic solid tumor" (score=6);
"AIDS/HIV" (score=6);
Each patient was given an individual score based on the sum of their comorbidities' score.

- diabetes-related complications (nephropathy/renal failure, neuropathy and retinopathy)
- other medication classes (antihyperlipidemic drugs, antihypertensives, antithrombotics and corticosteroids)
- drugs associated with acute pancreatitis- using a more updated classification (DiPiro, 2017)- Class I drugs (Definite association): 5-aminosalicylic acid/mesalamine/mesalazine, asparaginase, azathioprine, bortezomib, carbamazepine, cimetidine, corticosteroids, cisplatin, cytarabine, didanosine, enalapril, erythromycin, estrogens, furosemide, hydrochlorothiazide, mercaptopurine, octeotride, olsalazine, opiates, pentamidine, pentavalent antimonials, sulfasalazine, sulfamethoxazole-trimethoprim, sulindac, tamoxifen, tetracycline, valproic acid/salts. Class II drugs (Probable association): acetaminophen/paracetamol, atorvastatin, hydrochlorothiazide, ifosfamide, interferon alfa 2b, maprotiline, methyldopa, oxaliplatin, simvastatin.
- History of pancreatic procedures (endoscopic retrograde cholangiopancreatography - ERCP)

8.3. Data Sources

The Truven Marketscan Commercial database captures person-specific clinical utilization, expenditures, and enrolment across inpatient, outpatient, prescription drug, and carve-out services from a selection of large employers, health plans, and government and public organizations. This database links paid claims and encounter data to detailed patient information across sites and types of providers, and over time. The annual medical databases include private sector health data from approximately 100 payers. Historically, more than 500 million claim records are available in the database. The Commercial Claims and Encounters Database represents the medical experience of insured employees and their dependents for active employees, early retirees, patients with supplemental insurance (known as "COBRA continues"), and their dependents insured

by employer-sponsored plans (i.e., non-Medicare eligible). The data are HIPAA compliant thus all patients have been anonymized (Hansen, 2012).

The Truven Marketscan Commercial database offers several distinct advantages over other types of data sources such as large sample size; complete episodes of care; strong longitudinal tracking at patient level; and detailed prescription drug information. All of them have been described in the protocol (GSK Document number 2014N211972_00).

8.4. Study size

In May 2017, 5,651 patients with two consecutive exposures to albiglutide were identified in the Truven database, triggering the start of our study analysis. However, once we applied all the inclusion and exclusion criteria, the total number of albiglutide users was slightly less than expected.

Our final study population comprised N=247,543 diabetics meeting the inclusion criteria and among them at the beginning of the study 3,582 subjects were taking as new ADA albiglutide; 36,206 subjects were taking other GLP-1; 58,439 subjects were taking DPP4 inhibitor; and 149,316 subjects were taking other ADA. During the study period, from 15th April 2014 until 30th September 2016, 356 subjects switched off from albiglutide, and 1,300 subjects switched on, giving an approximate number of 4,882 subjects exposed to albiglutide in our study.

According to the sample size estimated in the protocol (GSK Document number 2014N211972_00), our study would have 80% power to detect a 2.5-fold increase in the risk of acute pancreatitis in subjects exposed to albiglutide compared to other antidiabetic agents.

8.5. Data Management

The database used for this study was Truven Marketscan Commercial (formerly, Thomson Reuters) insurance database. The data are de-identified and compliant with U.S. privacy laws.

8.5.1. Data transformation (Data handling conventions)

Data was extracted from an existing database, Truven Marketscan Commercial.

8.5.2. Resourcing needs

A PhD level Epidemiologist at GSK oversaw the conduct of the analysis and was responsible for producing the study reports and other deliverables related to the study.

Biostatistical and methodological issues were addressed by a senior level statistician at GSK with expertise in observational data

The analysis was conducted by one primary analyst and one independent quality check (QC) analyst from GSK skilled in population-based analyses, using SAS.

8.6. Data analyses

8.6.1. Essential analyses

The baseline demographic and clinical characteristics of the study groups (albiglutide, GLP-1 agonists excluding albiglutide, GLP-1 agonists including albiglutide, DPP-4 inhibitors and other ADA) have been described using frequencies (%) for categorical variables and mean (standard deviation) for continuous variables. The differences in the baseline characteristics between the five study groups (pairwise comparisons to other ADA) were assessed by chi-square test for categorical variables and *t*-test for continuous variables. A *p*-value of <0.05 was considered statistically significant (Table 1).

Unadjusted incidence rates (along with 95% confidence intervals) of acute pancreatitis were calculated for the albiglutide, GLP-1 agonists excluding albiglutide, GLP-1 agonists including albiglutide, DPP-4 inhibitors and the other ADA groups from the number of subjects who develop acute pancreatitis divided by the total person-years of follow-up in each group (Table 2). Follow-up for a specific study group started on the date of the index ADA in subjects who had at least six-months of follow-up in the database prior to the index ADA prescription until the first occurrence of any of the following:

1. Acute pancreatitis
2. Loss of pharmacy benefits
3. Disenrollment from the database
4. Subjects turning 65 years. Subjects 65 and older become eligible for Medicare coverage and may purchase other insurance coverage that is not captured in this database.
5. Discontinuation of the index medication (last refill date + days of supply on the last refill + 30 days)
6. Switching of the study medication groups (GLP-1 agonist users starting DPP-4 inhibitors, DPP-4 inhibitor users starting GLP-1 agonists or other ADA users starting GLP-1 agonists or DPP-4 inhibitors), or
7. End of follow up in the database.

The differences between the five study groups in terms of time to acute pancreatitis was assessed using Kaplan Meier survival curves with log rank test (Table 3, Figure 2a and Figure 2b).

Cox Proportional Hazards modeling was used to compare the adjusted risk of acute pancreatitis for each of the five exposure groups separately against the other ADAs (reference group) (Table 4), after checking that the proportional hazards assumptions were met.

All analyses were conducted using SAS version 9 (SAS institute).

8.6.2. Exploratory analyses

Due to restrictions with the number of albiglutide users who developed an acute pancreatitis, secondary analyses proposed in the protocol were not conducted for this interim report.

8.6.3. General considerations for data analyses

The Cox Proportional Hazards models were adjusted for comorbid conditions and exposures known to be associated with increased risk of pancreatitis that might also influence the choice of antidiabetic therapy (see Section 8.2.3 Confounders and effect modifiers).

We checked for any obvious inconsistencies in the data at the analysis stage. For example, a subject who had no diagnostic claim for obesity but was receiving prescriptions for a weight loss agent was considered obese.

8.6.4. Amendments to the statistical analysis plan

No further amendments were made to the statistical analysis plan as a result of the analyses conducted to produce this interim study report.

8.7. Quality control and quality assurance

The analysis was conducted by one primary analyst and one independent QC analyst from GSK skilled in population-based analyses, using SAS. The analysts followed GSK's standard operating procedures in terms of generating a Project Information Document (PID) which operationalizes the study variables and the steps and SAS programs involved in the analysis, using updated ICD-9 and ICD-10 coding lists and other quality standards that are in place.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Ethical approval and subject consent

Ethical approval or subject consent was not necessary for this study since the Truven Marketscan Commercial (formerly, Thomson Reuters) health insurance database is deidentified and HIPPA compliant.

9.2. Subject confidentiality

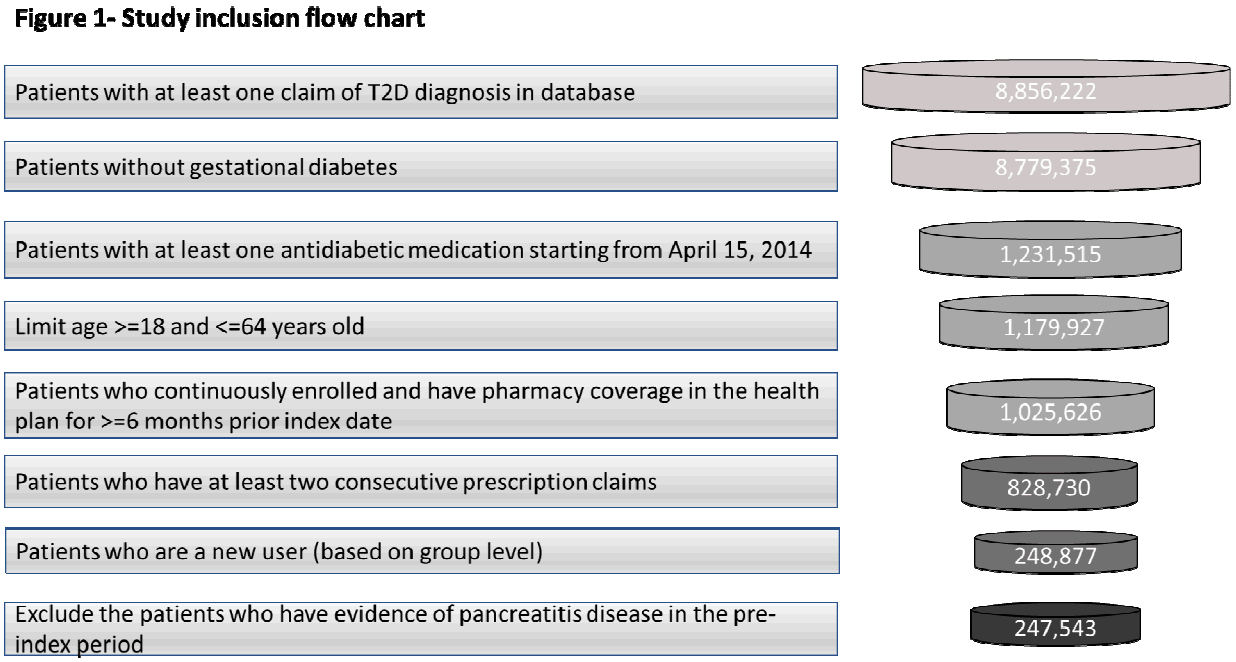
Since the data were deidentified, none of the study subjects' identity could be uncovered. Hence, the information on all subjects will remain confidential.

10. RESULTS

10.1. Descriptive data including baseline characteristics

We identified 1,231,515 patients in the Truven Marketscan Commercial database who had at least one antidiabetic medication starting from 15th April 2014, and after applying the inclusion/exclusion criteria our final study population was N=247,543 patients (see Figure 1 with a flow chart).

Figure 1 Study Inclusion Flow Chart



The study population was classified according to the index ADA prescription into the five exposure groups: Albiglutide; GLP-1 without albiglutide; all GLP-1; DPP-4 and 'Other ADA' and their baseline characteristics are described in Table 1.

Age and gender distribution was similar in all groups, although slightly more women were using albiglutide and/or GLP-1 (53% vs 47%), and more men were taking DPP-4 (55% vs 45%) or 'Other ADA' (52% vs 48%).

The majority of users came from the South region, about 71% for albiglutide users and around 50% of the other exposure groups, followed by the North Central one with about 12% of albiglutide users and about 20% of the other exposure groups.

The most common comorbidities observed in the study population were hypertension and hyperlipidaemia, followed by obesity and neuropathy. The albiglutide users showed the highest percentage of people with those comorbidities, followed by the GLP-1 users, and then DPP-4 and 'Other ADA' respectively. For example, while 71.4% of albiglutide users presented hypertension, there were about 66.4% of GLP-1 users, 63.6% of DPP-4 users and 50.8% of 'other ADA' users presenting the same.

The Charlson Comorbidity Index (CCI) was ≥ 2 for 38% of albiglutide users, about 32% of DPP-4 users and 24% of 'Other ADA' users.

The use of antihypertensive drugs and statins was common in all exposure groups, and higher in albiglutide users (see Table 1).

Table 1 Baseline characteristics of study groups according to the index antidiabetic agent (ADA)

	Albiglutide N=3,582		GLP-1 agonists excluding albiglutide N=36,206		GLP-1 agonists including albiglutide N=39,788		DPP-4 inhibitor N=58,439		Other ADA N=149,316
Baseline Characteristics	**n(%)**	**P value**	**n(%)**	**P value**	**n(%)**	**P value**	**n(%)**	**P value**	**n(%)**
Age									
18-34 years	66 (1.84)	<.0001	802 (2.22)	<.0001	868 (2.18)	<.0001	988 (1.69)	<.0001	5,685 (3.81)
35-44 years	407 (11.36)		4,286 (11.84)		4,693 (11.80)		5,931 (10.15)		17,998 (12.05)
45-54 years	1,199 (33.47)		12,320 (34.03)		13,519 (33.98)		18,624 (31.87)		47,486 (31.80)
55-64 years	1,910 (53.32)		18,798 (51.92)		20,708 (52.05)		32,896 (56.29)		78,147 (52.34)
Sex									
Males	1,697 (47.38)	<.0001	17,125 (47.3)	<.0001	18,822 (47.31)	<.0001	32,188 (55.08)	<.0001	76,969 (51.55)
Females	1,885 (52.62)		19,081 (52.7)		20,966 (52.69)		26,251 (44.92)		72,347 (48.45)
Region									
Northeast	300 (8.38)	<.0001	5,790 (15.99)	<.0001	6,090 (15.31)	<.0001	10,508 (17.98)	<.0001	24,885 (16.67)
North Central	423 (11.81)		7,102 (19.62)		7,525 (18.91)		10,586 (18.11)		29,402 (19.69)
West	310 (8.65)		4,206 (11.62)		4,516 (11.35)		6,273 (10.73)		18,590 (12.45)
South	2,536 (70.80)		18,637 (51.47)		21,173 (53.21)		30,238 (51.74)		74,172 (49.67)
Unknown	13 (0.36)		471 (1.30)		484 (1.22)		834 (1.43)		2,267 (1.52)

	Albiglutide N=3,582		GLP-1 agonists excluding albiglutide N=36,206		GLP-1 agonists including albiglutide N=39,788		DPP-4 inhibitor N=58,439		Other ADA N=149,316
Baseline Characteristics	**n(%)**	**P value**	**n(%)**	**P value**	**n(%)**	**P value**	**n(%)**	**P value**	**n(%)**
Comorbidities									
Neuropathy	864 (24.12)	<.0001	7,872 (21.74)	<.0001	8,736 (21.96)	<.0001	9,507 (16.27)	<.0001	20,041 (13.42)
Nephropathy	428 (11.95)	<.0001	3,808 (10.52)	<.0001	4,236 (10.65)	<.0001	5,164 (8.84)	<.0001	8,456 (5.66)
Retinopathy	298 (8.32)	<.0001	2,886 (7.97)	<.0001	3,184 (8.00)	<.0001	3,665 (6.27)	<.0001	6,446 (4.32)
Hypertension	2,558 (71.41)	<.0001	24,037 (66.39)	<.0001	26,595 (66.84)	<.0001	37,159 (63.59)	<.0001	75,832 (50.79)
Myocardial infarction	26 (0.73)	0.0026	383 (1.06)	0.0002	409 (1.03)	<.0001	727 (1.24)	0.3147	1,940 (1.30)
Heart failure	71 (1.98)	0.8573	744 (2.05)	0.1580	815 (2.05)	0.1669	1,239 (2.12)	0.0083	2,897 (1.94)
Ischemic Heart Disease	315 (8.79)	<.0001	3,064 (8.46)	<.0001	3,379 (8.49)	<.0001	4,694 (8.03)	<.0001	10,115 (6.77)
Cerebrovascular disease	66 (1.84)	0.0013	504 (1.39)	0.0196	570 (1.43)	0.0023	865 (1.48)	<.0001	1,850 (1.24)
Cardiac dysrhythmia	165 (4.61)	0.4682	1,807 (4.99)	0.3396	1,972 (4.96)	0.4793	3,033 (5.19)	0.0025	7,272 (4.87)
Biliary disease	39 (1.09)	0.7098	345 (0.95)	0.2163	384 (0.97)	0.2863	637 (1.09)	0.1921	1,531 (1.03)
Chronic liver disease	128 (3.57)	0.0142	1,418 (3.92)	<.0001	1,546 (3.89)	<.0001	2,052 (3.51)	<.0001	4,298 (2.88)
Hyperlipidaemia	2,497 (69.71)	<.0001	24,060 (66.45)	<.0001	26,557 (66.75)	<.0001	36,307 (62.13)	<.0001	70,886 (47.47)
Obesity	890 (24.85)	<.0001	9,640 (26.63)	<.0001	10,530 (26.47)	<.0001	9,517 (16.29)	<.0001	21,169 (14.18)
Alcoholism	21 (0.59)	0.1844	213 (0.59)	0.0001	234 (0.59)	0.0001	420 (0.72)	0.1271	1,170 (0.78)
Hypercalcemia	46 (1.28)	<.0001	290 (0.80)	<.0001	336 (0.84)	<.0001	381 (0.65)	<.0001	631(0.42)
Hyperparathyroidism	26 (0.73)	0.5471	205 (0.57)	0.0919	231 (0.58)	0.1539	349 (0.60)	0.2232	962(0.64)

	Albiglutide N=3,582		GLP-1 agonists excluding albiglutide N=36,206		GLP-1 agonists including albiglutide N=39,788		DPP-4 inhibitor N=58,439		Other ADA N=149,316
Baseline Characteristics	**n(%)**	**P value**	**n(%)**	**P value**	**n(%)**	**P value**	**n(%)**	**P value**	**n(%)**
Hypoglycaemia	121 (3.38)	<.0001	1,306 (3.61)	<.0001	1,427 (3.59)	<.0001	1,594 (2.73)	<.0001	3,413 (2.29)
Charlson Comorbidity Index score									
Mean(SD)	1.82 (1.54)	<.0001	1.76 (1.49)	<.0001	1.76 (1.49)	<.0001	1.64 (1.53)	<.0001	1.30(1.49)
0	257 (7.17)	<.0001	2,850 (7.87)	<.0001	3,107 (7.81)	<.0001	5,560 (9.51)	<.0001	38,463 (25.76)
1	1,962 (54.77)		20,037 (55.34)		21,999 (55.29)		34,299 (58.69)		74,485 (49.88)
>=2	1,363 (38.05)		13,319 (36.79)		14,682 (36.9)		18,580 (31.79)		36,368 (24.36)
Baseline other drugs									
Beta blockers	916 (25.57)	<.0001	9,301 (25.69)	<.0001	10,217 (25.68)	<.0001	13,634 (23.33)	<.0001	25,979 (17.40)
Calcium channel blockers	627 (17.50)	<.0001	5,864 (16.20)	<.0001	6,491 (16.31)	<.0001	9,061 (15.51)	<.0001	17,553 (11.76)
ACE inhibitors	1,176 (32.83)	<.0001	12,263 (33.87)	<.0001	13,439 (33.78)	<.0001	18,734 (32.06)	<.0001	29,349 (19.66)
Angiotensin receptor blockers	631 (17.62)	<.0001	6,098 (16.84)	<.0001	6,729 (16.91)	<.0001	8,635 (14.78)	<.0001	14,676 (9.83)
Diuretics	731 (20.41)	<.0001	7,922 (21.88)	<.0001	8,653 (21.75)	<.0001	10,083 (17.25)	<.0001	20,660 (13.84)
Combinations of the above	916 (25.57)	<.0001	8,181 (22.6)	<.0001	9,097 (22.86)	<.0001	12,568 (21.51)	<.0001	23,420 (15.68)
Other antihypertensive drugs	159 (4.44)	<.0001	1,436 (3.97)	<.0001	1,595 (4.01)	<.0001	2,178 (3.73)	<.0001	4,297 (2.88)
Statins	2,290 (63.93)	<.0001	22,281 (61.54)	<.0001	24,571 (61.75)	<.0001	32,814 (56.15)	<.0001	53,698 (35.96)
Fibrates	453 (12.65)	<.0001	4,372 (12.08)	<.0001	4,825 (12.13)	<.0001	6,025 (10.31)	<.0001	8,098 (5.42)
Bile acid sequestrants	63 (1.76)	<.0001	541 (1.49)	<.0001	604 (1.52)	<.0001	684 (1.17)	<.0001	1,110 (0.74)
Antithrombotic drugs	336 (9.38)	<.0001	3,278 (9.05)	<.0001	3,614 (9.08)	<.0001	5,159 (8.83)	<.0001	9,948 (6.66)

	Albiglutide N=3,582		GLP-1 agonists excluding albiglutide N=36,206		GLP-1 agonists including albiglutide N=39,788		DPP-4 inhibitor N=58,439		Other ADA N=149,316
Baseline Characteristics	**n(%)**	**P value**	**n(%)**	**P value**	**n(%)**	**P value**	**n(%)**	**P value**	**n(%)**
Corticosteroids	692 (19.32)	0.0114	7,098 (19.60)	<.0001	7,790 (19.58)	<.0001	10,135 (17.34)	0.0658	26,406 (17.68)
Drugs associated with pancreatitis									
class 1 drugs	1,799 (50.22)	<.0001	17,965 (49.62)	<.0001	19,764 (49.67)	<.0001	25,537 (43.70)	<.0001	61,684 (41.31)
class 2 drugs	2,168 (60.52)	<.0001	21,480 (59.33)	<.0001	23,648 (59.44)	<.0001	31,976 (54.72)	<.0001	58,020 (38.86)
History of pancreatic procedures (ERCP)									
Pancreatitis surgery	0(0.00)	0.0729	34(0.09)	0.8132	34(0.09)	0.7986	56(0.10)	0.6800	134(0.09)

Note: Statistic test is a pairwise comparison between each of the study groups and 'other ADA'

10.2. Results of essential analysis

The highest crude incidence rate of acute pancreatitis (per 1,000 person years) was observed among the 'Other ADA' users 1.3 (1.30, 1.31) whereas the lowest incidence rate was observed among the albiglutide users 1.2 (1.16, 1.25). Three cases of acute pancreatitis were found among albiglutide users, but the follow-up time was much shorter, about a tenth of the length of follow-up in the other groups

Table 2 Unadjusted incidence rate of acute pancreatitis

	Acute pancreatitis events (n)	Follow up time (Person-years)	Incidence rate (Per 1000 person-years) 95%CI
Albiglutide	3	2,494	1.2029 (1.1603, 1.2467)
GLP-1 excluding albiglutide	35	27,117	1.2907 (1.2772, 1.3043)
GLP-1 including albiglutide	38	29,611	1.2833 (1.2704, 1.2963)
DPP4- inhibitor	56	45,275	1.2369 (1.2267, 1.2472)
Other antidiabetic	137	104,843	1.3067 (1.2998, 1.3137)

The differences between the 5 study groups in terms of time to acute pancreatitis was assessed using Kaplan Meier survival curves with log rank test. In Figure 2a, we

considered albiglutide and the rest of the GLP-1 drugs in separate groups, and in Figure 2b we considered all GLP-1 drugs together in one group

The log-rank test results (P=0.9755 in Figure 2a; P=0.9092 in Figure 2b) indicate no significant difference between the time to acute pancreatitis for the exposure groups.

Figure 2 Kaplan-Meier Curves Comparing Four Study Groups

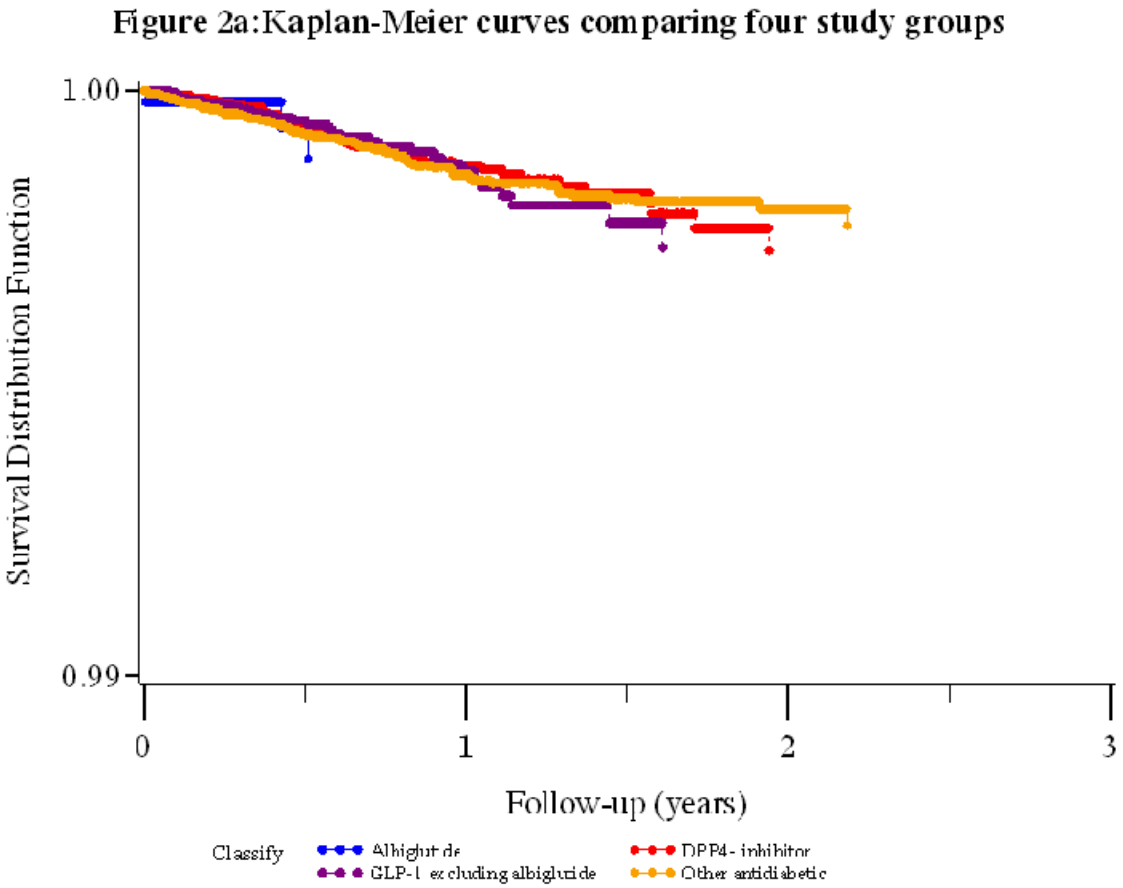
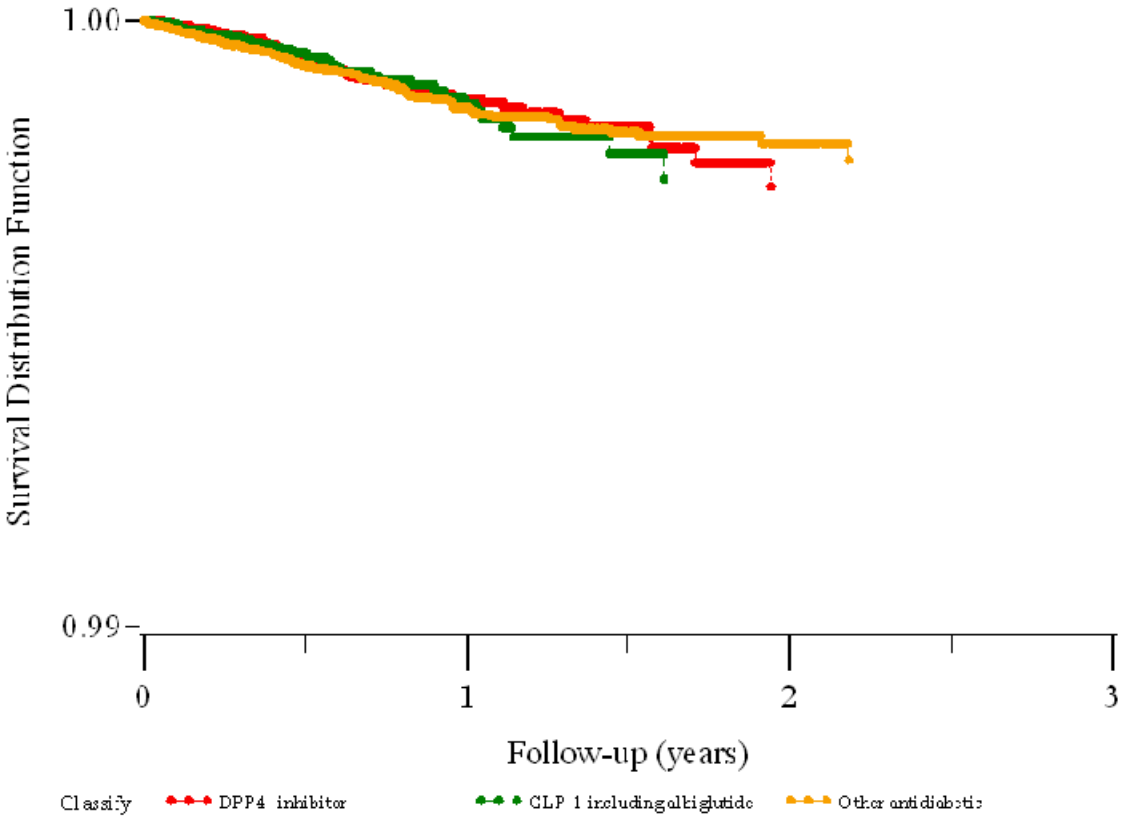


Figure 2b: Kaplan-Meier curves comparing three study groups



The mean (SD) time to event among albiglutide users was the lowest 115 (99) days, followed by 'other ADA' users with 168 (149) days, please see Table 3 below.

Table 3 Time to acute pancreatitis among the various groups (days)

Exposure group	Acute pancreatitis events (n)	Time to event (Days) Mean (SD)	Median (Interquartile range)
Albiglutide	3	115 (99)	156 (2, 186)
GLP-1 excluding albiglutide	35	201 (152)	169 (67, 328)
GLP-1 including albiglutide	38	194 (149)	163 (67, 302)
DPP4- inhibitor	56	209 (163)	157 (93, 270)
Other antidiabetic	137	168 (149)	132 (57, 255)

This summary is among patients who had acute pancreatitis events.

Cox Proportional Hazards modeling were used to compare the adjusted risk of acute pancreatitis among subjects treated with albiglutide, GLP-1 agonists excluding

albiglutide, GLP-1 agonists including albiglutide, and DPP-4 inhibitors compared to other ADA (reference group) (Table 4a among 4 exposure groups and Table 4b among 3 exposure groups: GLP-1, DPP-4 and Other ADA).

In the adjusted model, the use of albiglutide [hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.27 to 2.73], GLP-1 with and without albiglutide [0.91(0.63, 1.33); 0.92 (0.62, 1.35) respectively] and DPP-4 [0.90 (0.65, 1.24)], compared to other ADA was not associated with an increased risk of acute pancreatitis.

Some comorbidities like congestive heart failure, chronic liver disease or alcohol abuse, were associated with a 2.4 increased risk of developing acute pancreatitis.

Similarly, the use of pancreatitis level I drugs and fibrates showed an increased risk of developing acute pancreatitis of 1.69 (1.24, 2.29) and 2.67 (1.89, 3.77) respectively.

Table 4 Cox proportional hazard model for acute pancreatitis (on treatment) among 4 study groups

a)

Cohort Group	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Other ADA	Reference	.		.
Albiglutide	0.8841 (0.2815, 2.7770)	0.8330	0.8626 (0.2726, 2.7295)	0.8014
GLP-1 agonists (excluding Albiglutide)	0.9678 (0.6674, 1.4034)	0.8631	0.9156 (0.6212, 1.3495)	0.6558
DPP4- inhibitor	0.9355 (0.6855, 1.2767)	0.6742	0.9006 (0.6537, 1.2408)	0.5221
Age as of Index Date		.	0.9816 (0.9661, 0.9973)	0.0216
Northeast (ref=south)		.	0.9214 (0.6231, 1.3624)	0.6816
North Central (ref=south)		.	1.2550 (0.9071, 1.7363)	0.1703
West (ref=south)		.	1.0855 (0.7147, 1.6487)	0.7005
Unknown (ref=south)		.	1.7311 (0.5481, 5.4675)	0.3497
Charlson comorbidity score		.	1.0494 (0.9578, 1.1499)	0.3005
Neuropathy		.	1.0478 (0.7326, 1.4985)	0.7983

Cohort Group	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Retinopathy		.	0.5782 (0.2812, 1.1889)	0.1364
Nephropathy		.	1.1113 (0.6756, 1.8280)	0.6777
Hypertension		.	1.0191 (0.7497, 1.3853)	0.9041
Myocardial Infarction		.	1.0763 (0.4079, 2.8400)	0.8820
Congestive Heart failure		.	2.3618 (1.2164, 4.5855)	0.0111
Ischemic Heart Disease		.	1.1909 (0.7158, 1.9813)	0.5011
Cerebrovascular Disease		.	1.3347 (0.5317, 3.3508)	0.5387
Cardiac Dysrhythmia		.	0.7790 (0.4300, 1.4112)	0.4100
Gall Bladder Disease		.	1.8039 (0.8166, 3.9847)	0.1446
Chronic Liver Disease		.	2.3492 (1.4269, 3.8676)	0.0008
Obesity		.	1.0509 (0.7439, 1.4845)	0.7784
Alcohol Abuse		.	2.4082 (1.0312, 5.6236)	0.0423
Hyperlipidaemia		.	0.7384 (0.5510, 0.9894)	0.0422
Hypercalcemia		.	1.1180 (0.2700, 4.6296)	0.8777
Hyperparathyroidism		.	1.5552 (0.4680, 5.1679)	0.4711
Hypoglycaemia		.	0.8027 (0.3522, 1.8295)	0.6011
Beta Blockers		.	1.2792 (0.9151, 1.7881)	0.1497
Calcium Channel Blockers		.	1.0619 (0.7178, 1.5708)	0.7638

Cohort Group	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Diuretics		.	0.7765 (0.5160, 1.1687)	0.2253
Ace Inhibitors		.	1.2891 (0.9436, 1.7612)	0.1106
Angiotensin Receptor Blockers		.	0.5995 (0.3601, 0.9982)	0.0492
Combinations of the above		.	0.8980 (0.5779, 1.3954)	0.6322
Other antihypertensive drugs		.	1.2317 (0.6506, 2.3317)	0.5222
Anti Thrombotic Drugs		.	0.9484 (0.5749, 1.5646)	0.8358
Corticosteroids		.	0.8435 (0.5880, 1.2101)	0.3554
Pancreatitis Level 1 Drugs		.	1.6881 (1.2444, 2.2900)	0.0008
Pancreatitis Level 2 Drugs		.	0.7523 (0.5181, 1.0925)	0.1348
Fibrates		.	2.6686 (1.8915, 3.7650)	<.0001
Bile Acid Sequestrants		.	1.8682 (0.7661, 4.5556)	0.1694
Statins		.	0.9465 (0.6664, 1.3443)	0.7588

b)

Cohort Group	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Other ADA	Reference	.		.
GLP-1 agonists (including Albiglutide)	0.9606 (0.6702, 1.3767)	0.8265	0.9112 (0.6251, 1.3282)	0.6287
DPP4- inhibitor	0.9361 (0.6860, 1.2775)	0.6772	0.9007 (0.6538, 1.2408)	0.5222
Age as of Index Date		.	0.9816 (0.9661, 0.9973)	0.0216

Cohort Group	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Northeast (ref=south)		.	0.9219 (0.6236, 1.3629)	0.6836
North Central (ref=south)		.	1.2557 (0.9078, 1.7369)	0.1690
West (ref=south)		.	1.0860 (0.7150, 1.6493)	0.6989
Unknown (ref=south)		.	1.7326 (0.5486, 5.4716)	0.3489
Charlson comorbidity score		.	1.0494 (0.9578, 1.1499)	0.3005
Neuropathy		.	1.0476 (0.7325, 1.4983)	0.7988
Retinopathy		.	0.5782 (0.2812, 1.1890)	0.1364
Nephropathy		.	1.1113 (0.6756, 1.8279)	0.6778
Hypertension		.	1.0190 (0.7496, 1.3852)	0.9045
Myocardial Infarction		.	1.0765 (0.4079, 2.8405)	0.8817
Congestive Heart failure		.	2.3618 (1.2164, 4.5855)	0.0111
Ischemic Heart Disease		.	1.1908 (0.7158, 1.9812)	0.5013
Cerebrovascular Disease		.	1.3345 (0.5316, 3.3503)	0.5389
Cardiac Dysrhythmia		.	0.7791 (0.4301, 1.4113)	0.4102
Gall Bladder Disease		.	1.8037 (0.8166, 3.9843)	0.1446
Chronic Liver Disease		.	2.3494 (1.4270, 3.8678)	0.0008
Obesity		.	1.0509 (0.7440, 1.4846)	0.7780
Alcohol Abuse		.	2.4084 (1.0313, 5.6241)	0.0422

Cohort Group	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Hyperlipidaemia		.	0.7384 (0.5510, 0.9894)	0.0422
Hypercalcemia		.	1.1175 (0.2699, 4.6277)	0.8782
Hyperparathyroidism		.	1.5551 (0.4680, 5.1677)	0.4711
Hypoglycaemia		.	0.8028 (0.3522, 1.8296)	0.6012
Beta Blockers		.	1.2792 (0.9151, 1.7882)	0.1496
Calcium Channel Blockers		.	1.0618 (0.7178, 1.5707)	0.7641
Diuretics		.	0.7766 (0.5160, 1.1687)	0.2253
Ace Inhibitors		.	1.2892 (0.9437, 1.7613)	0.1105
Angiotensin Receptor Blockers		.	0.5995 (0.3601, 0.9982)	0.0492
Combinations of the above		.	0.8978 (0.5778, 1.3951)	0.6317
Other antihypertensive drugs		.	1.2317 (0.6506, 2.3316)	0.5222
Antithrombotic Drugs		.	0.9484 (0.5749, 1.5646)	0.8358
Corticosteroids		.	0.8435 (0.5880, 1.2101)	0.3554
Pancreatitis Level 1 Drugs		.	1.6881 (1.2444, 2.2900)	0.0008
Pancreatitis Level 2 Drugs		.	0.7524 (0.5182, 1.0926)	0.1350
Fibrates		.	2.6687 (1.8916, 3.7651)	<.0001
Bile Acid Sequestrants		.	1.8684 (0.7662, 4.5561)	0.1693
Statins		.	0.9464 (0.6663, 1.3441)	0.7582

10.3. Adverse events/adverse reactions

N/A

11. DISCUSSION

11.1. Interpretations of Results

Among five exposure groups, age, gender and geographical area were similarly distributed.

Comorbidities and medications were similarly distributed among exposure groups, except for a higher percentage of comorbidities/comedications being present in the albiglutide group than in the rest. The mean (SD) Charlson comorbidity index score was 1.82 (1.54) for albiglutide, compared to 1.76 (1.49), 1.64 (1.53) and 1.30 (1.49) for GLP-1, DPP-4 and other ADA respectively. This is expected as albiglutide is a third line treatment option in patients with T2D mellitus, and some comorbidities might be related to the progression of the disease.

As primary objective, this study has evaluated the association between albiglutide and acute pancreatitis compared to the use of other ADAs (excluding GLP-1 agonists and DPP-4 inhibitors) and our results did not yield any increased risk associated with albiglutide and acute pancreatitis.

We did neither observe an increased risk of acute pancreatitis associated with GLP-1 agonists (including and excluding albiglutide) nor with DPP-4 inhibitors as compared to the use of other ADAs.

There are some controversial results in the literature about the hypothesis that acute pancreatitis risk is increased with incretin-based therapy use. Our results are in line with other observational studies cited previously (Garg, 2010, Dore, 2009, Romley, 2012, Wenten, 2012, Funch, 2013 and Li, 2013) in that we did not find an increased risk of pancreatitis. They also concur with two meta-analyses where the odds ratio (OR) of GLP-1 agonists on acute pancreatitis was OR=1.01 (0.37, 2.76) (Monami, 2014a) and DPP-4 inhibitors OR=0.89 (0.32, 2.49) (Monami, 2014b).

However, other studies (Singh, 2013) have found an increased risk of acute pancreatitis associated with the use of GLP-1-based therapies, adjusted odds ratio (AOR)=2.24 (1.36, 3.68).

There are many reasons why findings in observational studies may differ, and one can be the design employed. In our study, we took into account the potential medication changes over the study period, with a time varying analysis, and this might explain differences observed with other studies where the risk of developing acute pancreatitis is associated with the first drug prescription in the study period without considering subsequent switches.

This study compares the risk of acute pancreatitis with non-GLP-1, non DPP-4 other ADA medications, which included a mix of preferred treatments such as metformin,

second line treatments, and third and fourth line treatments such as insulin. It might be possible that insulin users were at higher risk of acute pancreatitis than metformin users, reflecting the underlying severity of the disease, but the risk of the comparator group would be compensated with the mix of users, and since we are comparing with third line treatment drugs (albiglutide and GLP-1 agonists) and second line treatment drugs (DPP-4 inhibitors) the mix of treatments make a suitable comparison.

11.2. Limitations

This study, being observational in nature, was subject to various types of bias that affect observational studies.

For example, given the heightened awareness of the potential risk of pancreatitis in subjects exposed to the GLP-1 agonists, pancreatitis may be more likely to be diagnosed and recorded in subjects exposed to GLP-1 agonists compared to other antidiabetic agents (ascertainment bias). This could result in observing a false positive association between GLP-1 agonists and pancreatitis. That is, the results could be biased towards observing an association which does not exist.

Alternatively, physicians may be more likely to avoid prescribing GLP-1 agonists in subjects with a history or family history of pancreatitis given precautionary product labelling guidance. This could result in false negative findings, i.e., no association between GLP-1 agonists and pancreatitis is observed when one exists, given that the drug is used in subjects with a very low risk of pancreatitis.

We were relying on ICD-9 and ICD-10 diagnostic codes to capture acute pancreatitis. There was no ascertainment of the outcome through medical record review. This could have resulted in outcome misclassification, given that some ICD-9 /10 diagnostic codes did not reflect confirmed cases of pancreatitis but were rule-out diagnoses. Outcome misclassification could have biased the results towards the null, i.e., no association was observed when one exists.

Polypharmacy (e.g. other anti-diabetic agents, lipid lowering therapy, antihypertensive therapy, antiplatelet therapy) and switching of medications inherent to this patient population complicates efforts to assign attribution to specific medications. It is difficult to disentangle the effect of each drug on the outcome of interest when subjects are exposed to multiple drugs simultaneously.

Other limitations include:

- Some drugs associated with increased risk of pancreatitis, e.g. paracetamol, are available over the counter and were therefore not captured in this study. Thus, the observed association could be due to an exposure other than the study drug that was not captured, biasing the results towards observing an association that did not exist.

- The study results are generalizable to the commercial health insurance population under the age of 65 years from which the study population was derived as well as others with similar characteristics but may not be generalized to the uninsured or those covered by government insurance programs for the indigent or those older than 65 years of age.

- Some important confounders, such as duration and severity of diabetes, body mass index, glycemic control (HbA1c level), diet and exercise were not captured in the database and hence were not adjusted for in the analyses. Such confounders may partially explain an association, if one was observed but were not accounted for in the study. This could bias the results towards observing an association that was not due to the drug but could be explained by other confounders such as BMI.

- Exposure was inferred from prescription claims. A prescription claim for an ADA does not necessarily mean that the patient consumed the drug and is a surrogate measure of drug exposure. This could result in exposure misclassification, i.e., subjects who did not consume the drug were categorized as exposed to the drug, biasing the results towards the null, i.e., missing an association if one existed.

- Although we controlled for hyperlipidemia, obesity and other confounders proposed under confounders (Section 8.2.3), as identified by medical claims, these claims were inconsistently coded. Therefore, some confounders mentioned above were not well captured. This could bias the results towards observing an association that was not due to the drug but could be explained by other confounders such as hyperlipidemia.

12. CONCLUSIONS

In summary, the interim results of our study suggest that compared with use of any other ADAs not including GLP-1s or DPP-4s, neither the use of albiglutide nor the use of incretin based drugs in general, is associated with an increased risk of acute pancreatitis among patients with T2D.

The cohort size of albiglutide users was only powered to rule out an increased risk of 2.5; therefore another, final analysis is planned per protocol when the number of albiglutide exposures reaches N=31,000.

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