TITLE PAGE

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Title:	An Observational Study of the Risk of Common Malignant Neoplasms and Malignant Neoplasms of Special Interest (Thyroid and Pancreatic Cancer) in Subjects Prescribed Albiglutide Compared to Those Prescribed Other Antidiabetic Agents

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Subject: Albiglutide, Common Malignant Neoplasms, Thyroid Cancer, Pancreatic Cancer

Author(s): [redacted] and [redacted]

PASS information

Title	An Observational Study of the Risk of Common Malignant Neoplasms and Malignant Neoplasms of Special Interest (Thyroid and Pancreatic Cancer) in Subjects Prescribed Albiglutide Compared to Those Prescribed Other Antidiabetic Agents
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Marketing authorisation holder(s)	GlaxoSmithKline
Joint PASS	No

Research question and objectives	This study compares the risk of malignant neoplasms of special interest (thyroid and pancreatic cancer) in subjects prescribed albiglutide, and albiglutide in combination with insulin, to other antidiabetic agent and insulin, respectively. It also compares the risk of the most common malignant neoplasms (breast, prostate, colorectal and lung) in subjects prescribed albiglutide in combination with insulin compared to insulin.
Country(-ies) of study	Retrospective observational analysis conducted in a UK database, CPRD.
Author	[redacted] PhD Sr Dir Epidemiology WW Epidemiology RD Projects Clinical Platforms & Sciences GSK 1250 S. Collegeville Road, Collegeville, Pennsylvania, 19426-0989, United States Email [redacted] Tel [redacted]

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	GlaxoSmithKline Research & Development Limited 980 Great West Road Brentford Middlesex, TW8 9GS UK
MAH contact person	[redacted]

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

ADA	Antidiabetic agent
AE	Adverse Event
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
GSK	GlaxoSmithKline
RR	Relative risk
T2DM	Type 2 diabetes mellitus

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Oseni
Tradjenta
Victoza

1. RESPONSIBLE PARTIES

[redacted] PhD

Sr Dir Epidemiology

WW Epidemiology

RD Projects Clinical Platforms & Sciences

GSK

1250 S. Collegeville Road, Collegeville, Pennsylvania, 19426-0989, United States

Email [redacted]

Tel [redacted]

SPONSOR SIGNATORY:

[redacted] 11/18/2015
Primary Author/ Project officer Date

[redacted] 18/11/2015
Therapy Area Leader Date

SPONSOR INFORMATION PAGE

WWEpi Project Identifier: PRJ2331

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Sponsor Contact Address

GlaxoSmithKline Research & Development Limited
1250 South Collegeville Road
Collegeville, PA 19426, USA
Telephone Number: [redacted]

Sponsor Medical Monitor Contact Information: Not applicable

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2. ABSTRACT

Title: An Observational Study of the Risk of Common Malignant Neoplasms and Malignant Neoplasms of Special Interest (Thyroid and Pancreatic Cancer) in Subjects Prescribed Albiglutide Compared to Those Prescribed Other Antidiabetic Agents

Rationale and background: GLP-1 receptor agonists have been associated with an increased incidence of thyroid C-cell focal hyperplasia and C-cell adenomas and carcinomas in rodents. The mechanism and clinical relevance of GLP-1 receptor agonist induced thyroid C-cell tumours in rodents are unclear and an association between GLP-1 receptor agonist therapy and the development of medullary thyroid cancer in man has not been observed.

The potential for incretin-based therapies such as DPP-4 inhibitors and GLP-1 receptor agonists to impact the risk of pancreatic neoplasia in both the acinar/ductal and islet cell compartments have been raised due to an increased prominence of pancreatic ductal dilatation that has been described in pancreatic autopsy tissue from adults with type 2 diabetes mellitus (T2DM) receiving incretin-based therapy.

The potential role of hypersinsulinemia and exogenous insulin therapy to contribute to an increased risk of cancer has been extensively investigated; epidemiological studies of insulins have yielded conflicting results and a recent outcome study of insulin glargine did not observe an increased incidence of malignancy.

In the albiglutide Phase III program including studies of up to 3 years duration, the cumulative incidence for any neoplasm was similar between treatment groups, and no single event or group of similar events, including pancreatic and thyroid cancers, appeared to occur at a meaningfully different rate between treatments.

Nevertheless, as albiglutide is a newly marketed GLP-1 receptor agonist and it is not possible to fully resolve the questions that have been raised, it is important to further characterize what, if any, impact albiglutide therapy (with or without insulin) may have on the risk of malignant neoplasms, including thyroid and pancreatic cancers, utilizing real world data.

The proposed study addresses an important safety question for the GLP-1 receptor agonist class of antidiabetic agents in general and for albiglutide in particular using a population based datasource.

Research Questions and Objectives: The objectives of this study are:

1. To compare the risk of malignant neoplasms of special interest (thyroid and pancreatic cancer) in subjects prescribed albiglutide, compared to other antidiabetic agents.
2. To compare the risk of malignant neoplasms of special interest (thyroid and pancreatic cancer) in subjects prescribed albiglutide in combination with insulin, compared to insulin.

3. To compare the risk of the most common malignant neoplasms (breast, prostate, colorectal and lung) in subjects prescribed albiglutide in combination with insulin, compared to insulin.

Secondary objective:

1. To assess the relationship between the dose and duration of exposure to albiglutide and malignant neoplasms of special interest.

Study Design: Case-control study nested within a diabetes cohort (nested case-control study).

Population:

Study Cohort: The diabetes cohort will include type 2 diabetic subjects aged ≥ 18 years old at cohort entry and who had at least three consecutive new prescriptions ("new users") for the same antidiabetic agent (ADA) in the Clinical Practice Research Datalink (CPRD) as of when albiglutide will be fully launched in the U.K. Cohort entry is defined as the date of the first prescription for the new antidiabetic agent. Subjects with a history of the malignant neoplasms of special interest or a history of the common malignant neoplasms prior to cohort entry will be excluded.

Subjects will be followed until a first-ever diagnosis of a malignant neoplasm of special interest, the common malignant neoplasms, death from any cause, end of registration with a general practice (patient transfers out of the practice), end of practice contribution of data to CPRD, end of data collection in CPRD, or end of study period.

Case and Control Subject Selection:

Nested case-control analyses will be conducted within the defined cohort. All incident cases of malignant neoplasm of special interest and the common malignant neoplasms occurring during follow-up will be identified.

Up to 5 control subjects, randomly selected from the risk set of eligible control subjects, will be matched to each patient on age (±2 years), sex, general practice, calendar year of cohort entry, and duration of follow-up.

Variables:

Outcome Definitions: Common malignant neoplasms (breast, prostate, colorectal and lung) and malignant neoplasms of special interest including pancreatic and thyroid cancer will be captured using Read Codes.

Exposure Definitions: The primary exposure definition will be "ever exposed", defined as receiving at least three consecutive prescriptions of the ADA of interest between cohort entry and the 3 months before the index date.

Antidiabetic exposure among cases and controls will be classified according to prescriptions received from cohort entry until the 3 months prior to the index date into the following mutually exclusive categories:

1. Ever exposed to albiglutide (with or without oral antidiabetic agents; without insulin)
2. Ever exposed to albiglutide in combination with insulin (with or without oral antidiabetic agents)
3. Ever exposed to other GLP-1 receptor agonists (excluding albiglutide; with or without oral antidiabetic agents; without insulin)
4. Ever exposed to other GLP-1 receptor agonists in combination with insulin (excluding albiglutide; with or without oral antidiabetic agents)
5. Ever exposed to DPP-4 inhibitors (with or without other oral antidiabetic agents; without insulin)
6. Ever exposed to DPP-4 inhibitors in combination with insulin (with or without other oral antidiabetic agents)
7. Ever exposed to other ORAL ADA (excluding DPP-4 inhibitors; without insulin)
8. Ever exposed to insulin (alone or in combination with oral ADA, excluding GLP-1 receptor agonists and DPP-4 inhibitors).

Additional categories combining 1 and 2 (Ever exposed to albiglutide), 3 and 4 (Ever exposed to GLP-1 receptor agonists excluding albiglutide), 1, 2, 3 and 4 (Ever exposed to GLP-1 receptor agonists including albiglutide), 5 and 6 (Ever exposed to DPP-4 inhibitors), and 7 and 8 (ever exposed to antidiabetic agents other than GLP-1 receptor agonists and DPP-4 inhibitors) will be created.

Data Source: The study will be conducted using the Clinical Practice Research Datalink (CPRD). This database provides an opportunity to capture albiglutide exposure in one of the European countries in which albiglutide will launch. This database provides longitudinal follow-up on a representative sample of the U.K. general population. The cancer ascertainment rates in this database are comparable to the U.K. cancer registries.

Study Size: The aim is to conduct the analysis when approximately 10,000 albiglutide prescribed subjects, with minimum follow-up duration of one year each, have accrued in the database. We will assess cumulative exposure to albiglutide in CPRD in late 2017/ early 2018. If approximately 10,000 subjects with a minimum of 1 year follow-up each have accrued, we will conduct the analysis. We will (1) extend the duration of the study to assess any malignancy risk up to 60 months of starting ADA therapy and (2) extend the study should the malignancy rates be lower than those reported by Staa, 2012 if a plausible signal for an increased risk of cancer was observed in the study.

Data analysis: The characteristics of the pancreatic cancer, thyroid cancer and the most common malignant neoplasms (breast, prostate, colorectal and lung) case subjects and matched control subjects will be described using descriptive statistics.

Given the nested case-control design, conditional logistic regression will be used to estimate odds ratios along with 95% confidence intervals (CIs) of the malignant neoplasms of special interest and the common malignant neoplasms associated with the use of albiglutide compared to other antidiabetic agents. Separate conditional logistic regression models will be run for the various objectives of the study, providing likelihood ratios for the cancers of special interest as well as the most common malignant neoplasms. For the cancers of special interest, subjects ever exposed to albiglutide will be compared to subjects exposed to other antidiabetic agents. For the common malignant neoplasms, subjects ever exposed to albiglutide in combination with insulin will be compared to those exposed to insulin.

Milestones: A major milestone was the submission of study protocol to PRAC in September of 2014. An updated version addressing PRAC's comments was submitted in February 2015. An updated version addressing PRAC's outstanding questions from MAH response to request for supplementary information was submitted in June 2015. Cumulative exposure to albiglutide in CPRD will be assessed starting late 2017/early 2018 to trigger analysis start if adequate size and duration of albiglutide exposure have accrued per study sample above. We will provide these data on a semi-annual basis as part of the PASS Progress Report to be submitted with the PBRER starting in May 2018.

3. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	February 5, 2015	Various Sections	Updates marked in final track-changes version	Address PRAC's comments and feedback received November 21, 2014
2	June 22, 2015	Various Sections	Updates marked in final track-changes version	Address PRAC's comments and feedback received April 28, 2015
3	November 27, 2015	Milestones	Updates marked in green and strike-through text in final track-changes version	Address PRAC's comments and feedback received October 24, 2015 and finalize the protocol

4. MILESTONES

Milestone	Planned date
Submission of study protocol to PRAC	September 17, 2014
Submission of updated protocol to PRAC	February 5, 2015
Submission of updated protocol to PRAC	June 2015
Provide counts of albiglutide subjects in CPRD	Every 6 months starting in May 2018 as part of PASS Progress Report with the PRBER.
Start of data analysis	Contingent on albiglutide counts; potentially 2018
Repeat data analysis	Contingent on 1) extending the duration of the study to assess any malignancy risk up to 60 months of starting ADA therapy and (2) extending the study should the malignancy rates be lower than those reported by Staa, 2012 if a plausible signal for an increased risk of cancer was observed in the study
Submission of preliminary analysis to PRAC	Six months post start of data analysis
Final report of study results	Nine months post start of data analysis

5. RATIONALE AND BACKGROUND

5.1. 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-1R, 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.

Epidemiologic evidence suggests that people with diabetes are at significantly higher risk for many forms of cancer (Giovannucci, 2010). The results of a review of several meta-analyses (Vigneri, 2009) indicated that some cancers develop more commonly in patients with diabetes (predominantly type 2), while prostate cancer occurs less often in men with diabetes. The relative risks imparted by diabetes are greatest (about twofold or higher) for cancers of the liver, pancreas, and endometrium, and lesser (about 1.2–1.5 fold) for cancers of the colon, rectum, breast, and bladder. According to Vigneri and colleagues, only prostate cancer is associated with a lower risk in men with diabetes. There is some data to also suggest that hyperinsulinemia in diabetes patients may be associated with cancer progression and tumor growth based on studies that have shown increased insulin

receptor expression in breast, lung and colon cancer cells. Evidence for other cancers has been inconclusive (e.g., kidney, non-Hodgkin lymphoma) or is lacking.

Diabetes-related factors including steatosis, nonalcoholic fatty liver disease, and cirrhosis may enhance susceptibility to liver cancer. With regard to pancreatic cancer, interpretation of the causal nature of the association is complicated by the fact that abnormal glucose metabolism may be a consequence of pancreatic cancer (so-called "reverse causality"). However, a positive association between diabetes and pancreatic cancer risk has also been found when restricted to patients with diabetes that precedes the diagnosis of pancreatic cancer by 5 years or more, so reverse causation does not likely account for the entirety of the association.

There has been extensive discussion and investigation into the possible impact of different anti-diabetic therapies on the risk of malignancies in general and on specific types of cancers in adults with diabetes (Giovannucci, 2010). The potential role of hyperinsulinemia and exogenous insulin therapy to contribute to an increased risk of cancer has also been extensively investigated; epidemiological studies of insulins have yielded conflicting results and a recent outcome study of insulin glargine did not observe an increased incidence of malignancy (Gerstein, 2012).

GLP-1 receptor agonists have been associated with an increased incidence of thyroid C-cell focal hyperplasia and C-cell adenomas and carcinomas in rodents. The mechanism and clinical relevance of GLP-1 receptor agonist induced thyroid C-cell tumours in rodents are unclear and an association between GLP-1 receptor agonist therapy and the development of medullary thyroid cancer in man has not been observed (Parks, 2010). Dore, 2012 assessed the potential for an association of thyroid cancer with exenatide using claims data and found there was an increased risk of thyroid malignancies with exenatide use [relative risk (RR) 1.4; 95% confidence interval (CI) 0.8−2.4], but when the data were analyzed using inpatient claims, no increase in risk was observed (RR 0.9; 95% CI 0.3–2.6). In clinical trials with liraglutide, a higher incidence of papillary thyroid carcinoma, a thyroid non C-cell tumor, was reported with liraglutide compared to other treatments (1.5 versus 0.5 per 1000 patient-years) (Victoza USPI, 2013).

The potential for incretin-based therapies such as DPP-4 inhibitors and GLP-1 receptor agonists to impact the risk of pancreatic neoplasia in both the acinar/ductal and islet cell compartments have been raised due to an increased prominence of pancreatic ductal dilatation that has been described in pancreatic autopsy tissue from adults with T2DM receiving incretin-based therapy (Butler, 2013) as well as some rodent studies. Questions regarding the pancreas safety profile of incretin based therapies have been extensively discussed in the medical and scientific literature and like the data, opinions have been varied.

In 2013, the US and EU regulatory authorities conducted independent reviews of the pancreas safety of the incretin based therapies. Based on their reviews of all available nonclinical and clinical data, inclusive of academic and pharmaceutical company investigations, both the US and EU regulatory agencies have concluded that while data are currently not available to support a final conclusion on the long term pancreatic safety of incretin therapies, an association between GLP-1 receptor agonist therapy and the

development of pancreatic cancers has not been observed (EMA, 2013; Egan, 2014) and both authorities have noted that additional insights are anticipated from the ongoing cardiovascular outcome studies and from ongoing pharmcoepidemologic research.

In the albiglutide Phase III program including studies of up to 3 years duration, the cumulative incidence for any neoplasm was similar between treatment groups and no single event or group of similar events, including pancreatic and thyroid cancers, appeared to occur at a meaningfully different rate between treatments.

Nevertheless, as albiglutide is a newly marketed GLP-1 receptor agonist and it is not possible to fully resolve the questions that have been raised, it is important to further characterize what, if any, impact albiglutide therapy (with or without insulin) may have on the risk of malignant neoplasms, including thyroid and pancreatic cancers, utilizing real world data.

5.2. Rationale

The proposed study addresses an important safety question for the GLP-1 receptor agonist class of antidiabetic agents in general and for albiglutide in particular, using a population based datasource. Pancreatic and thyroid cancers are cancers of special interest for the class of GLP-1 receptor agonists. To investigate the potential risk of malignancies more broadly, this study also includes an assessment of the more common cancers of breast, prostate, colorectal and lung in subjects prescribed albiglutide in combination with insulin.

6. RESEARCH QUESTION AND OBJECTIVE(S)

The objectives of this study are:

1. To compare the risk of malignant neoplasms of special interest (thyroid and pancreatic cancer) in subjects prescribed albiglutide compared to other antidiabetic agents.
2. To compare the risk of malignant neoplasms of special interest (thyroid and pancreatic cancer) in subjects prescribed albiglutide in combination with insulin compared to insulin.
3. To compare the risk of the most common malignant neoplasms (breast, prostate, colorectal and lung) in subjects prescribed albiglutide in combination with insulin compared to insulin.

Secondary objective:

1. To assess the relationship between the dose and duration of exposure to albiglutide and malignant neoplasms of special interest.

7. RESEARCH METHODS

7.1. Study Design

Case-control study nested within a diabetes cohort (nested case-control study).

Study Cohort: The diabetes cohort will include type 2 diabetic subjects aged ≥ 18 years old at cohort entry and who had at least three consecutive new prescriptions ("new users") for the same antidiabetic agent (ADA) in the Clinical Practice Research Datalink (CPRD) when albiglutide will be fully launched in the U.K.

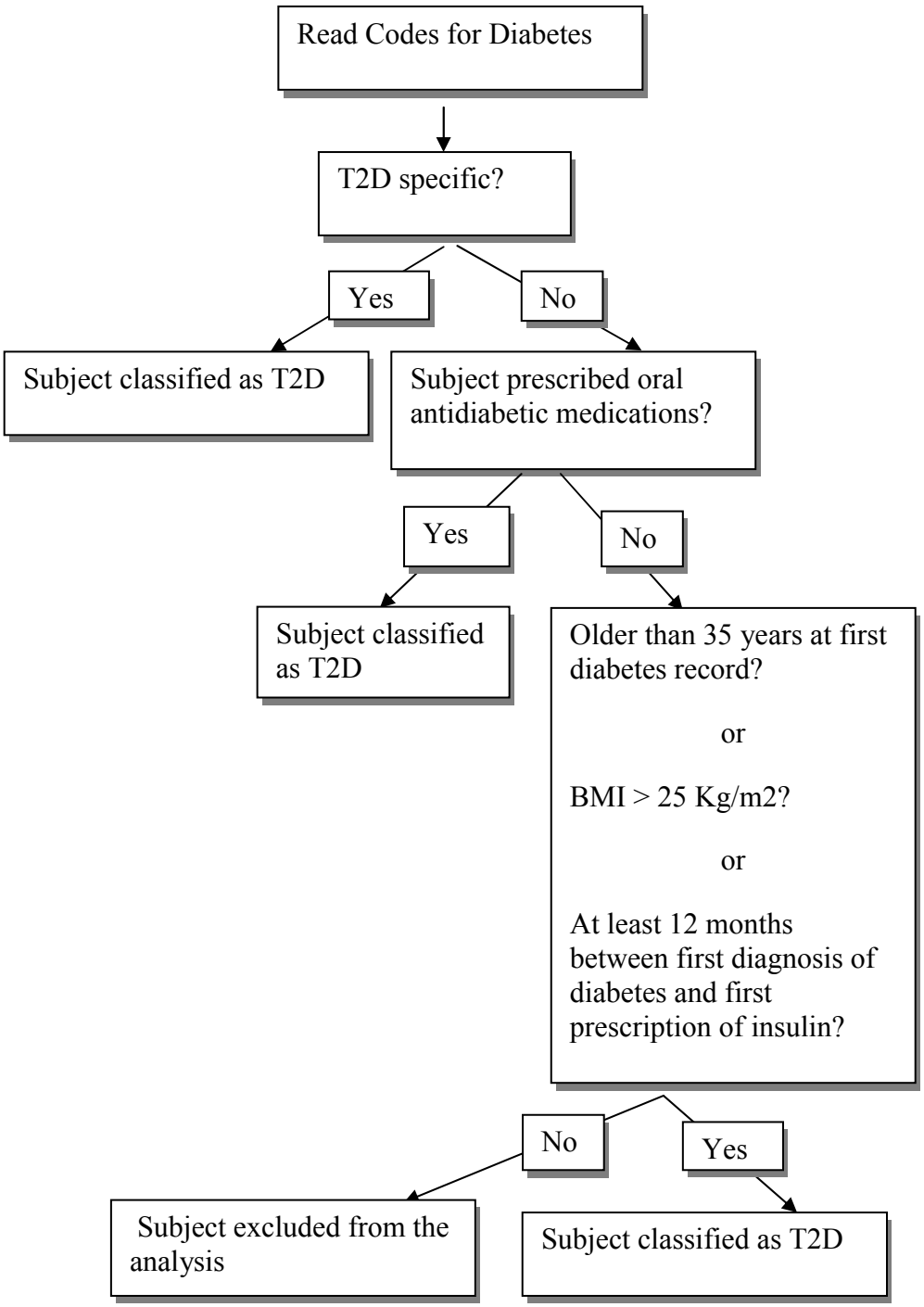
A list of Read diagnostic codes for Diabetes is included as ANNEX 3. Some of the codes are specific for type 2 diabetes and others do not distinguish between type 1 diabetes and type 2 diabetes. For type 2 diabetes specific codes, subjects with those codes will be classified as type 2 diabetes patients. For codes that are not specific, the antidiabetic medications prescribed will be used to aid in the determination of the type of diabetes. Subjects prescribed oral antidiabetic agents (with or without insulin) at any point during their follow-up in the CPRD will be classified as having type 2 diabetes. For subjects who are prescribed insulin therapy alone, type 2 diabetes will be assumed for those with diabetes related records who are also older than 35 years at first diabetes record or who have a high BMI (greater than 25 Kg/m2) or who have at least 12 months between first diagnosis of diabetes and first prescription of insulin. Where the diagnosis remains unclear, subjects will be excluded from the analysis. This algorithm is outlined in Figure 1.

A subject will be considered a new user of an ADA if there was no evidence of prescriptions for that ADA ingredient in the database in the three months prior to cohort entry. Cohort entry is defined as the date of the first prescription for the new antidiabetic agent. All patients included in the study will be from "up-to-standard" general medical practices, thus meeting CPRD research quality standards, and will be required to have at least 3 months of medical history in the CPRD before their cohort entry.

Subjects with a history of malignant neoplasm of special interest or a history of the common malignant neoplasms prior to cohort entry will be excluded.

Subjects will be followed until a first-ever diagnosis of a malignant neoplasm of special interest, the common malignant neoplasms, death from any cause, end of registration with a general practice (patient transfers out of the practice), end of practice contribution of data to CPRD, end of data collection in CPRD, or end of study period.

Figure 1 Algorithm for Classification of Diabetes



Case and Control Subject Selection:
Nested case-control analyses will be conducted within the defined cohort. All incident cases of malignant neoplasms (common and of special interest) occurring during follow-up will be identified on the basis of Read diagnostic codes, which is the standard clinical terminology system used in general practice in the U.K.

For cases and controls with type 2 diabetes, the earliest date of diabetes related diagnosis or earliest date of a prescription for an anti-diabetic agent in CPRD, whichever comes first, will be considered the date of diabetes diagnosis. The date of each case subject's earliest most common malignant neoplasm (breast, prostate, colorectal and lung) or malignant neoplasm of special interest diagnosis will defined as the index date. For the purposes of the analyses, only case subjects with at least 3-months of follow-up prior to their malignancy diagnosis will be retained to allow for a minimum of 3-month latency period prior to the malignant neoplasm diagnosis (Smiechowski, 2013). Up to 5 control subjects, randomly selected from the risk set of eligible control subjects, will be matched to each patient on age (±2 years), sex, general practice, calendar year of cohort entry, and duration of follow-up. Cases that have at least one control will be kept in the analysis. Cases that could not be matched to any controls will be excluded from the analysis. Control subjects will be assigned the same index date as the cases to which they are matched, thus ensuring that case subjects and matched control subjects had equal duration of follow-up before the index date. By definition, all control subjects will be alive, not previously diagnosed with malignant neoplasms (common or of special interest), and registered with a general practice when matched to a given case subject.

7.2. Setting

We propose to conduct this study using the CPRD. This database provides longitudinal follow-up on a representative sample of the U.K. general population. The cancer ascertainment rates in this database are comparable to U.K. cancer registries. The CPRD has been extensively utilized for pharmacoepidemiologic research.

The albiglutide launch plans for the various European countries is currently under development and will be influenced by the reimbursement decisions made by the authorities in those countries and assessments made by GSK. These decisions and assessments could influence GSK's ability to launch in the respective countries. The most recent albiglutide launches were in Spain and Belgium. Decisions relating to launches in UK, Italy, France, Germany and other European countries will be made in 2015 and 2016 and will inform our ability to assess and utilize databases available in these countries.

The ultimate decision regarding our ability to utilize the CPRD depends upon feasibility assessments conducted following the launch of albiglutide in the U.K. If the use of the CPRD was not feasible, we will conduct this study using other data sources such as the US based Truven Marketscan Commercial database that is proposed for the pancreatitis study. However, CPRD or other similar data sources would be preferred if feasible because of the greater longitudinal follow-up and because it is electronic health record (EHR) based rather than reimbursement claims-based.

7.3. Variables

7.3.1. Outcome definitions

Common malignant neoplasms (breast, prostate, colorectal and lung) and malignant neoplasms of special interest including pancreatic and thyroid cancer will be captured using Read Codes. Code lists will be generated prior to the conduct of the analysis and reviewed by a UK practicing clinician.

Cancer diagnoses have shown high validity in the CPRD, with sensitivities and positive predictive values exceeding 90% (García-Rodríguez, 2001, González-Pérez, 2005, Hall, 2005), resulting in case ascertainment rates comparable to U.K. cancer registries (Jick, 2003, Staa, 2012).

7.3.2. Exposure definitions

For both case and control subjects, all antidiabetic agents prescribed between cohort entry and the index date will be captured using CPRD's product coding system, Multilex, BNF. Code lists will be created and reviewed closer to the study start date in order to capture new drugs that may have come on the market. Exposures initiated in the 3-months before the index date will be excluded from the analysis to account for a latency time window, because these are unlikely to be associated with the outcome. The primary exposure definition will be "ever exposed", defined as receiving at least three consecutive prescription of the ADA of interest between cohort entry and the 3 months before the index date.

Antidiabetic exposure among cases and controls will be classified according to prescriptions received from cohort entry until the 3 months prior to the index date. The categorization of exposure will be prioritized to capture GLP-1 agonists first, followed by DPP-4 inhibitors, and then the other antidiabetic agents. The following mutually exclusive categories will be created:

1. Ever exposed to albiglutide (with or without oral antidiabetic agents; without insulin)
2. Ever exposed to albiglutide in combination with insulin (with or without oral antidiabetic agents)
3. Ever exposed to other GLP-1 receptor agonists (excluding albiglutide; with or without oral antidiabetic agents; without insulin)
4. Ever exposed to other GLP-1 receptor agonists in combination with insulin (excluding albiglutide; with or without oral antidiabetic agents)
5. Ever exposed to DPP-4 inhibitor (with or without other oral antidiabetic agents; without insulin)
6. Ever exposed to DPP-4 inhibitor in combination with insulin (with or without other oral antidiabetic agents)
7. Ever exposed to other ORAL ADA (excluding DPP-4 inhibitors; without insulin).

8. Ever exposed to insulin (alone or in combination with ADA, excluding GLP-1 receptor agonists and DPP-4 inhibitors).

GLP-1 receptor agonists are not usually prescribed in combination with DPP-4 inhibitors. Therefore these are treated as mutually exclusive in the specification of exposure categories. Patients in which these two classes are prescribed in combination will be excluded from the analysis.

The table below depicts the 8 mutually exclusive categories described with the values in the table reflecting the category numbers specified above:

ADA (other than insulin)	Insulin	
	No	Yes
albiglutide	1	2
other GLP-1 receptor agonists	3	4
DPP-4 inhibitors	5	6
oral ADA, no GLP-1 receptor agonist or DPP-4 inhibitor	7	8
no ADA except insulin		8

An additional category of "Ever exposed to albiglutide" will be created by combining categories 1 and 2 above.

An additional category of "Ever exposed to GLP-1 receptor agonists excluding albiglutide" will be created by combining categories 3 and 4 above.

An additional category of "Ever exposed to GLP-1 receptor agonists including albiglutide" will be created by combining categories 1, 2, 3 and 4 above.

An additional category of "Ever exposed to DPP-4 inhibitors" will be created by combining categories 5 and 6 above.

An additional category of "Ever exposed to antidiabetic agents" will be created by combining categories 7 and 8 above.

The GLP-1 receptor agonists included in this study will be albiglutide, exenatide and liraglutide. The DPP-4 inhibitors included in this study will be sitagliptin, saxagliptin, linagliptin, alogliptin, combination of sitagliptin and metformin (Janumet), and combination of sitagliptin and simvastatin (Juvisync), combinations of alogliptin and metformin (Kazano) and combinations of alogliptin and pioglitazone (Oseni). The analysis will allow for the inclusion of available data from all GLP-1 receptor agonists and DPP-4 inhibitors captured in the database at the time it is conducted.

For exposure to be classified as combination with insulin, the prescription dates for the ADA of interest and the prescription date for insulin has to overlap by at least 30 days.

In secondary (exploratory) exposure definitions, we will consider whether a relationship exist between the dose and duration of use of albiglutide and malignant neoplasms of special interest.

7.3.3. Confounders and effect modifiers

The analyses will be adjusted for comorbid conditions and exposures known to be associated with common malignant neoplasms and malignant neoplasms of special interest that might also influence the choice of antidiabetic therapy. These conditions and exposures known as confounders will be measured at any time from at least 3 months before cohort entry up to 3 months before the index date.
The following potential confounders will be adjusted for:

- Smoking status (ever, never, or unknown): Smoking status is well recorded in the CPRD but these records are not complete. The sensitivity and positive predictive value of the CPRD database for current smoking are 78% (95% CI: 52–94) and 70% (95% CI: 46–88) respectively. Current smoking rates in the CPRD were 79% of expected rates in comparison to a population-based survey (Lewis, 2004).
- BMI (≤30 vs. >30 kg/m^2): BMI is well recorded in the CPRD but these records are not complete. BMI will be further stratified into underweight (if applicable), normal, overweight and obese. A BMI of less than 18 will be considered underweight, a BMI of 18 or greater and less than 25 is normal, a BMI of 25 or greater and less than 30 is overweight and a BMI of 30 and above is considered obese.
- Excessive alcohol use: Defined based on a computerized diagnosis of alcoholism or of alcohol-related chronic disease (e. g., alcoholic cirrhosis, alcoholic cardiopathy).
- Level of glycated hemoglobin A1C (HbA1c): The latest recorded value that is at least 3 months before index date.
- Diabetes duration before cohort entry
- Exposure to radiation

7.4. Data sources:

We propose to use the U.K. Clinical Practice Research Datalink (CPRD), a longitudinal primary care electronic health records database, representing more than 13 million patients (as of Dec. 2013) from across the U.K. The CPRD is representative of the U.K. general population, with age and sex distributions comparable to those reported by the U.K. National Population Census (García Rodríguez, 1998). Information collected in the CPRD has been subjected to validation studies and been shown to contain consistent and high-quality data (Khan, 2010).

A study comparing the General Practice Research Database (GPRD) patient consulting rates for diabetes with equivalent data from the 4th National Morbidity Survey in General Practice suggested that the GPRD is a potentially useful source of national morbidity data (Hollowell, 1997).

Cancer diagnoses have shown high validity in the CPRD, with sensitivities and positive predictive values exceeding 90% (García-Rodríguez, 2001, González-Pérez, 2005, Hall, 2005, Jick, 2003), resulting in case ascertainment rates comparable to the U.K. cancer registries (Staa, 2012). The GPRD has been used to study the association between antidiabetic exposure and cancer. For example, (Smiechowski, et al. 2013) assessed the use of metformin and the incidence of lung cancer in patients with Type 2 Diabetes.

7.5. Study size

We aim to conduct the analysis when approximately 10,000 albiglutide prescribed subjects (anticipated 50% male and 50% female), with minimum follow-up duration of one year each, have accrued in the database.

The table below provides the relative risk increases with albiglutide exposure compared to other antidiabetic agents that could be detected with 80% power for the most common cancers as well at the cancers of special interest with a one sided alpha of 0.05% (given that the interest is in ruling out increased risks of malignancy with albiglutide exposure). It assumes that 5% of diabetic cohort will be exposed to albiglutide.

Relative risk increase with albiglutide exposure compared to other antidiabetic agents that could be detected with 80% power given 10,000 albiglutide exposed subjects each followed for a year.

Malignancy	**N of Albiglutide exposed subjects**	**Rate per 100 patient- years in the reference category** (Staa, 2012)	**Relative risk powered to detect**
Breast cancer	5,000 women	0.33	1.7
Prostate cancer	5,000 men	0.3	1.75
Colorectal cancer	10,000	0.18	1.75
Lung cancer	10,000	0.19	1.65
Pancreatic cancer	10,000	0.07	2.2

As can be seen from the table above, this study is powered to detect a 1.7 fold increased risk of the most common malignant neoplasms and a 2.2 fold increased risk of pancreatic cancer for albiglutide prescribed subjects compared to other antidiabetic agents.

Given that the incidence rate of thyroid cancer among diabetic subjects was not captured in the study by Staa et al., the rate provided by the publicly available World Health Organization (WHO) Globocan database (GLOBOCAN 2012 http://globocan.iarc.fr/) was utilized. This database reported an incidence rate of thyroid cancer in the U.K. of 6.2

– 6.5 per 100,000 in 2012 for the general population 60-69 years old (mean age for Staa et al. study is approximately 64 years). Given that the rate of thyroid cancer is not elevated in diabetic subjects compared to the general population, we utilized this rate in the general population to estimate the power of the study. This study is powered to detect a 5.7 fold increased risk of thyroid cancer for albiglutide prescribed subjects compared to other antidiabetic agents.

We will assess cumulative exposure to albiglutide in CPRD in late 2017/early 2018. If approximately 10,000 subjects with a minimum of 1 year follow-up each have accrued, we will conduct the analysis.

7.6. Data management

The database proposed for this study is the CPRD. The data are de-identified and compliant with the U.K. privacy laws.

7.6.1. Data handling conventions

Data will be extracted from an existing database, the CPRD.

7.6.2. Resourcing needs

The study is overseen by a senior PhD level Epidemiologist at GSK with over 40 metabolic disease- related publications in peer-reviewed journals. This epidemiologist will oversee the conduct of the analysis and be responsible for producing the study reports and other deliverables related to the study.

Biostatistical and methodological issues will be addressed by a senior level statistician at GSK with expertise in observational data. A senior level statistician has contributed to the development of the draft protocol and will continue to provide expertise and skills as needed during the conduct of the study.

The analysis will be independently conducted by 2 senior level GSK analysts skilled in population-based analyses, using SAS.

7.6.3. Timings of Assessment during follow-up

The aim is to conduct the analysis when approximately 10,000 albiglutide prescribed subjects, with minimum exposure duration of one year each, have accrued in the database. We will assess cumulative exposure in CPRD in late 2017/early 2018. If approximately 10,000 subjects with a minimum of 1 year exposure each have accrued, we will conduct the analysis.

We will (1) extend the duration of the study to assess any malignancy risk up to 60 months of starting ADA therapy and (2) extend the study should the malignancy rates be lower than those reported by Staa, 2012 if a plausible signal for an increased risk of cancer was observed in the study. Lower malignancy rates observed in the proposed study compared to those reported by Staa, 2012, would not seem to support the hypothesis that the introduction of GLP-1 receptor agonists into clinical practice has

contributed to an increased risk of cancer. Therefore, if the rates of malignancy were lower than those reported by Staa and there is a plausible signal for increased risk of common malignancy observed in the current study, then the MAH agrees it would be reasonable to consider modification to the study including the possibility of extending the duration of the study even further or other alternatives as appropriate.

7.7. Data analysis

7.7.1. Essential analysis

The baseline demographic and clinical characteristics of the diabetes study cohort will be described using frequencies (%) for categorical variables and mean (standard deviation) for continuous variables. The characteristics of the pancreatic cancer, thyroid cancer and most common malignant neoplasms (breast, prostate, colorectal and lung) case subjects and matched control subjects will be described using descriptive statistics (Table 1- Table 6).

Given the nested case-control design, conditional logistic regression will be used to estimate odds ratios along with 95% CIs of malignant neoplasms associated with the exposure to albiglutide compared to other antidiabetic agents. Separate conditional logistic regression models will be run for the various objectives as follows:

1. Model 1a and Model 1b corresponding to objective 1: All cases of pancreatic cancer (Model 1a) and thyroid cancer (Model 1b) and controls will be included. The likelihood of pancreatic cancer (Model 1a) and thyroid cancer (model 1b) in subjects exposed to albiglutide (exposure category 1 under exposure definitions) will be compared to that in subjects exposed to "other oral antidiabetic agents" (exposure category 7 under exposure definitions), adjusting for potential confounders (Table 7 and Table 8).
2. Model 2a and Model 2b corresponding to objective 2: All cases of pancreatic cancer (Model 2a) and thyroid cancer (Model 2b) and controls will be included. The likelihood of pancreatic cancer (Model 2a) and thyroid cancer (model 2b) in subjects ever exposed to albiglutide in combination with insulin (exposure category 2 under exposure definitions) will be compared to that in subjects exposed to insulin (exposure category 8 under exposure definitions), adjusting for potential confounders (Table 9 and Table 10).

An additional model (Model A Exp) combining models 1a and 2a will be run to provide an overall estimate of the likelihood of pancreatic cancer in subjects "ever exposed to albiglutide" compared to subjects exposed to other antidiabetic agents, if similar trends for both models are observed (Table 11).

An additional model (Model B Exp) combining models 1b and 2b will be run to provide an overall estimate of the likelihood of thyroid cancer in subjects ever exposed to albiglutide compared to subjects exposed to other antidiabetic agents, if similar trends for both models are observed (Table 12).

An additional model (Model C Exp) will be run to provide an overall estimate of the likelihood of pancreatic cancer in subjects "ever exposed to GLP-1 receptor agonists excluding albiglutide" compared to other antidiabetic agents (Table 13).

An additional model (Model D Exp) will be run to provide an overall estimate of the likelihood of thyroid cancer in subjects "ever exposed to GLP-1 receptor agonists excluding albiglutide" compared to other antidiabetic agents (Table 14).

An additional model (Model E Exp) will be run to provide an overall estimate of the likelihood of pancreatic cancer in subjects "ever exposed to GLP-1 receptor agonists" compared to other antidiabetic agents (Table 15).

An additional model (Model F Exp) will be run to provide an overall estimate of the likelihood of thyroid cancer in subjects "ever exposed to GLP-1 receptor agonists" compared to other antidiabetic agents (Table 16).

An additional model (Model G Exp) will be run to provide an estimate of the likelihood of pancreatic cancer in subjects "ever exposed to DPP-4 inhibitors" compared to other antidiabetic agents (Table 17).

An additional model (Model H Exp) will be run to provide an estimate of the likelihood of thyroid cancer in subjects "ever exposed to DPP-4 inhibitors" compared to other antidiabetic agents (Table 18).

3. Models 3a, 3b, 3c and 3d corresponding to objective 3: The most common malignant neoplasms (breast (model 3a), prostate (model 3b), colorectal (model 3c) and lung (model 3d)) cases and controls will be included. The likelihood of the most common malignant neoplasms individually in subjects ever exposed to albiglutide in combination with insulin (exposure category 2 under exposure definitions) will be compared to that in subjects ever exposed to insulin (exposure category 8, under exposure definitions), adjusting for potential confounders (Table 19- Table 22)

All the models above will utilize conditional logistic regression given the matched nested case-control design.

Two sensitivity analyses will be conducted to include 6 and 12 months latency periods prior to the malignant neoplasm diagnosis.

7.7.2. Exploratory analysis

Exploratory analysis will be conducted to address the secondary objective of the study, i.e., determine whether there is a relationship between duration of exposure to albiglutide and malignant neoplasms of special interest using number of prescriptions and cumulative duration of use. This analysis will not be undertaken if the primary analysis showed no association between albiglutide exposure and the risk of malignant neoplasms of special interest.

Therefore, among patients deemed to have been ever exposed to albiglutide in the primary exposure definition, we will investigate whether the likelihood of malignant

neoplasms of special interest varies with the total number of prescriptions received and the cumulative duration of exposure. The total number of albiglutide prescriptions will be tabulated by summing all albiglutide prescriptions received between cohort entry and index date. Cumulative duration will be calculated by summing the prescribed duration associated with each albiglutide prescription received between cohort entry and index date. Both variables will be categorized in quartiles, based on the distribution of use in the control subjects. The lowest quartile in each case will be used as the reference group:

1. Model 4a and Model 4b: All cases of pancreatic cancer (Model 4a) and thyroid cancer (Model 7b) and controls will be included. The likelihood of pancreatic cancer (Model 4a) and thyroid cancer (model 4b) in subjects in the top 3 quartiles of albiglutide exposure will be compared to that of subjects in the lowest quartile of albiglutide exposure, adjusting for potential confounders (Table 23 and Table 24).
2. Model 5a and Model 5b: All cases of pancreatic cancer (Model 5a) and thyroid cancer (Model 5b) and controls will be included. The likelihood of pancreatic cancer (Model 5a) and thyroid cancer (model 5b) in subjects in the top 3 quartiles of albiglutide in combination with insulin exposure will be compared to that of subjects in the lowest quartile of albiglutide in combination with insulin exposure, adjusting for potential confounders (Table 25 and Table 26).

An additional model (Model A Dur) combining models 4a and 5a will be run to provide an overall estimate of the effect of albiglutide duration of exposure on the likelihood of pancreatic cancer, if similar trends for both models are observed.

An additional model (Model B Dur) combining models 4b and 5b will be run to provide an overall estimate of the effect of albiglutide duration of exposure on the likelihood of thyroid cancer if similar trends for both models are observed.

Additional stratified analyses will be conducted for subjects using albiglutide 30 mg SC once weekly and 50 mg SC once weekly if the sample size allows.

7.7.3. General considerations for data analyses

Two general approaches will be used to adjust for potential confounders: matching and covariate adjustment. Cases and controls will be matched on age (±2 years), sex, general practice, calendar year of cohort entry, and duration of follow-up.

The conditional logistic regression models will be adjusted for comorbid conditions and exposures known to be associated with malignant neoplasms that might also influence the choice of antidiabetic therapy.

We will check for any obvious inconsistencies in the data at the analysis stage. For example, a subject who has no diagnostic code for smoking but is receiving smoking cessation treatment will be considered a smoker and a subject who has no diagnostic

claim for obesity but is receiving prescriptions for a weight loss agent will be considered obese.

7.8. Quality control

The analysis will be independently conducted by 2 senior level GSK analysts skilled in population-based analyses, using SAS. The analysts will follow 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 coding lists and other quality standards that are in place. The results produced by the two independent analysts will be reviewed for consistency. Any differences in results between the two will be reconciled. The independent analysis approach is in place to ensure that the protocol is interpreted and operationalized consistently and that the results of the analysis are constant across the 2 analyses, thus ensuring reliability of the study findings.

7.9. Limitations of the research methods

Drug use is inferred from automated prescribing data. We do not know if subjects dispense the prescriptions and consume them. However, this would be the case for the various antidiabetic agents and there is no reason to believe that it is different for one class compared to the other.

This study being observational in nature is subject to various types of bias that affect observational studies. For example, given the heightened awareness of the potential risk of pancreatic cancer in subjects exposed to the GLP-1 receptor agonists, such cancers are more likely to be diagnosed and recorded in subjects exposed to GLP-1 receptor agonists compared to other antidiabetic agents. Another example relates to channelling bias. Physicians are probably more likely to avoid prescribing GLP-1 receptor agonists in subjects with family history of pancreatic cancer. This can result in false positive finding in the former case and false negative findings in the later case.

Missing data can result in misclassification of the exposure or outcome of interest. Misclassification biases the findings of the study towards the null, i.e., missing an association if one exists. Missing data related to confounders can result in attributing the outcome of interest to an exposure when it is related to the confounder and not the exposure itself, resulting in false positive findings.

7.9.1. Study closure/uninterpretability of results

Not applicable

7.10. Other aspects

Not applicable

8. PROTECTION OF HUMAN SUBJECTS

8.1. Ethical approval and subject consent

The study protocol will be reviewed and approved by the [redacted] The data analyses can start only after approval is granted.

8.2. Subject confidentiality

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

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Will be carried out according to SOP SOP-BMD-3003 Safety Reporting from Epidemiology Studies and Analyses of Epidemiology Databases. This SOP applies to all GSK-sponsored observational studies and analyses of epidemiology data with safety-related primary objectives. It outlines the process and responsibilities with respect to global reporting of safety-related results of GSK-sponsored non-interventional, observational studies and is in compliance with Good Pharmacovigilance Practices (GVP) guidelines. It outlines the roles and responsibilities of the epidemiologist/study manager as it relates to PASS studies as well as individual adverse event case reports.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

10.1. Target Audience

The results will be disseminated externally via regulatory submission, manuscripts and abstracts.

10.2. Study reporting and publications

The results of the study will be disseminated through abstract submissions, publishing in a peer reviewed journal and posting on publically accessible GSK website, in accordance with GSK's policies.

Milestone for Data dissemination	**Planned Date**
Posting to GSK's Clinical Disclosure Register	Within 1 year of final report of study results
Manuscript submission	Within 1 year of final report of study results

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ANNEX 1. LIST OF TABLES

Tables

Table 16: Crude and adjusted likelihood of thyroid cancer in subjects ever exposed to GLP-1 receptor agonists compared to subjects exposed to other antidiabetic agents

Table 17: Crude and adjusted likelihood of pancreatic cancer in subjects ever exposed to DPP-4 inhibitors compared to subjects exposed to other antidiabetic agents

Table 18: Crude and adjusted likelihood of thyroid cancer in subjects ever exposed to DPP-4 inhibitors compared to subjects exposed to other antidiabetic agents

Table 19: Crude and adjusted likelihood of breast cancer in women ever exposed to albiglutide in combination with insulin compared to that in women ever exposed to insulin

Table 20: Crude and adjusted likelihood of prostate cancer in men ever exposed to albiglutide in combination with insulin compared to that in men ever exposed to insulin

Table 21: Crude and adjusted likelihood of colorectal cancer in subjects ever exposed to albiglutide in combination with insulin compared to that in subjects ever exposed to insulin

Table 22: Crude and adjusted likelihood of lung cancer in subjects ever exposed to albiglutide in combination with insulin compared to that in subjects ever exposed to insulin

Table 23: Crude and adjusted likelihood of pancreatic cancer in subjects in the top 3 quartiles of albiglutide exposure compared to that of subjects in the lowest quartile of albiglutide exposure

Table 24: Crude and adjusted likelihood of thyroid cancer in subjects in the top 3 quartiles of albiglutide exposure compared to that of subjects in the lowest quartile of albiglutide exposure

Table 25: Crude and adjusted likelihood of pancreatic cancer in subjects in the top 3 quartiles of albiglutide in combination with insulin exposure compared to that of subjects in the lowest quartile of albiglutide in combination with insulin exposure

Table 26: Crude and adjusted likelihood of thyroid cancer in subjects in the top 3 quartiles of albiglutide in combination with insulin exposure compared to that of subjects in the lowest quartile of albiglutide in combination with insulin exposure

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:				
1.1.1 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)	X	☐	☐	14
1.1.2 The objectives of the study?	X	☐	☐	14
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	X	☐	☐	15
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	X	☐	☐	14
1.2.3 if applicable, that there is no *a priori* hypothesis?	☐	☐	X	

Comments:

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	X	☐	☐	14
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	X	☐	☐	14

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.2.2 Age and sex?	X	☐	☐	17
2.2.3 Country of origin?	X	☐	☐	17
2.2.4 Disease/indication?	X	☐	☐	17
2.2.5 Co-morbidity?	X	☐	☐	17
2.2.6 Seasonality?	☐	☐	X	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	X	☐	☐	17

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	X	☐	☐	18
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	X	☐	☐	14
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	X	☐	☐	23
3.4 Is sample size considered?	X	☐	☐	21
3.5 Is statistical power calculated?	X	☐	☐	21

Comments:

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	X	☐	☐	18
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc)	X	☐	☐	18
4.1.3 Covariates?	X	☐	☐	20
4.2 Does the protocol describe the information				

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	X	☐	☐	18
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	X	☐	☐	18
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	X	☐	☐	20
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	X	☐	☐	15
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	X	☐	☐	18
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	X	☐	☐	18
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	X	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	X	☐	☐	18
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	X	☐	☐	18
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	X	☐	☐	18
5.4 Is exposure classified based on biological mechanism of action?	X	☐	☐	18
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	X	☐	☐	24

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	X	☐	☐	18
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	X	☐	☐	18

Comments:

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address: 7.1.1 Selection biases? 7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	 X X	 ☐ ☐	 ☐ ☐	 26 26
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	X	☐	☐	20
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	X	☐	☐	20
7.4 Does the protocol address other limitations?	X	☐	☐	26

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☐	X	☐	
8.2 Is the choice of statistical techniques described?	X	☐	☐	23
8.3 Are descriptive analyses included?	X	☐	☐	23
8.4 Are stratified analyses included?	X	☐	☐	25
8.5 Does the plan describe the methods for identifying:				

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.5.1 Confounders?	X	☐	☐	20
8.5.2 Effect modifiers?	☐	X	☐	
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	X	☐	☐	25
8.6.2 Effect modification?	☐	X	☐	

Comments:

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	X	
9.2 Are methods of quality assurance described?	X	☐	☐	26
9.3 Does the protocol describe quality issues related to the data source(s)?	X	☐	☐	26
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	X	☐	☐	21

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	X	☐	☐	12
9.5.2 Any progress report?	X	☐	☐	12
9.5.3 End of data collection?	X	☐	☐	12
9.5.4 Reporting? (i.e. interim reports, final study report)	X	☐	☐	12
9.6 Does the protocol include a section to document future amendments and deviations?	X	☐	☐	11
9.7 Are communication methods to disseminate results described?	X	☐	☐	27
9.8 Is there a system in place for independent review of study results?	X	☐	☐	27

Comments:

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	X	☐	☐	27
10.2 Has any outcome of an ethical review procedure been addressed?	☐	X	☐	
10.3 Have data protection requirements been described?	X	☐	☐	27

Comments:

Name of main author of study protocol: [redacted] _____

Date: / /

Signature: _____

ANNEX 3: READ Codes for Diabetes

9OL..00	Diabetes monitoring admin.
66A..00	Diabetic monitoring
66AS.00	Diabetic annual review
C10..00	Diabetes mellitus
9N1Q.00	Seen in diabetic clinic
C10F.00	Type 2 diabetes mellitus
9OL4.00	Diabetes monitoring 1st letter
66A2.00	Follow-up diabetic assessment
9NND.00	Under care of diabetic foot screener
66AP.00	Diabetes: practice programme
9OL1.00	Attends diabetes monitoring
66A4.00	Diabetic on oral treatment
68A7.00	Diabetic retinopathy screening
66AZ.00	Diabetic monitoring NOS
66AJ.00	Diabetic - poor control
C100112	Non-insulin dependent diabetes mellitus
66Ac.00	Diabetic peripheral neuropathy screening
9OL5.00	Diabetes monitoring 2nd letter
66A3.00	Diabetic on diet only
66Aq.00	Diabetic foot screen
C109.00	Non-insulin dependent diabetes mellitus
F420.00	Diabetic retinopathy
13B1.00	Diabetic diet
9OLA.00	Diabetes monitor. check done

7L19800	Subcutaneous injection of insulin
66AR.00	Diabetes management plan given
9h42.00	Excepted from diabetes quality indicators: Informed dissent
2G5E.00	O/E - Right diabetic foot at low risk
66A5.00	Diabetic on insulin
2G5I.00	O/E - Left diabetic foot at low risk
9h41.00	Excepted from diabetes qual indicators: Patient unsuitable
F420000	Background diabetic retinopathy
9N4I.00	DNA - Did not attend diabetic clinic
66AI.00	Diabetic - good control
C109.12	Type 2 diabetes mellitus
66AQ.00	Diabetes: shared care programme
66AD.00	Fundoscopy - diabetic check
8BL2.00	Patient on maximal tolerated therapy for diabetes
1434.00	H/O: diabetes mellitus
9OL6.00	Diabetes monitoring 3rd letter
66Ai.00	Diabetic 6 month review
9N1v.00	Seen in diabetic eye clinic
8CA4100	Pt advised re diabetic diet
2BBP.00	O/E - right eye background diabetic retinopathy
2BBQ.00	O/E - left eye background diabetic retinopathy
8B3l.00	Diabetes medication review
66A9.00	Understands diet - diabetes
66Ab.00	Diabetic foot examination
42W..00	Hb. A1C - diabetic control

66AU.00	Diabetes care by hospital only
9NM0.00	Attending diabetes clinic
8H7r.00	Refer to diabetic foot screener
8I3X.00	Diabetic retinopathy screening refused
2G5F.00	O/E - Right diabetic foot at moderate risk
2G5J.00	O/E - Left diabetic foot at moderate risk
66A1.00	Initial diabetic assessment
F420400	Diabetic maculopathy
66AW.00	Diabetic foot risk assessment
9OLA.11	Diabetes monitored
13AB.00	Diabetic lipid lowering diet
2BBM.00	O/E - diabetic maculopathy absent both eyes
ZC2C800	Dietary advice for diabetes mellitus
C100100	Diabetes mellitus, adult onset, no mention of complication
66Ao.00	Diabetes type 2 review
9OL8.00	Diabetes monitor.phone invite
9N4p.00	Did not attend diabetic retinopathy clinic
9N1i.00	Seen in diabetic foot clinic
14P3.00	H/O: insulin therapy
C101.00	Diabetes mellitus with ketoacidosis
66A8.00	Has seen dietician - diabetes
66AT.00	Annual diabetic blood test
C10FJ00	Insulin treated Type 2 diabetes mellitus
9OL3.00	Diabetes monitoring default
66AV.00	Diabetic on insulin and oral treatment

66A7.00	Frequency of hypo. attacks
9OL..11	Diabetes clinic administration
66AA.11	Injection sites - diabetic
66AH000	Conversion to insulin
8CS0.00	Diabetes care plan agreed
2G5G.00	O/E - Right diabetic foot at high risk
66AH.00	Diabetic treatment changed
2G5K.00	O/E - Left diabetic foot at high risk
9OLD.00	Diabetic patient unsuitable for digital retinal photography
F372.12	Diabetic neuropathy
F420600	Non proliferative diabetic retinopathy
C106.12	Diabetes mellitus with neuropathy
9OL7.00	Diabetes monitor.verbal invite
C106.00	Diabetes mellitus with neurological manifestation
8H4F.00	Referral to diabetologist
8I3W.00	Diabetic foot examination declined
68A9.00	Diabetic retinopathy screening offered
13AC.00	Diabetic weight reducing diet
F420100	Proliferative diabetic retinopathy
66AY.00	Diabetic diet - good compliance
C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
C109.13	Type II diabetes mellitus
C109.11	NIDDM - Non-insulin dependent diabetes mellitus
9OLZ.00	Diabetes monitoring admin.NOS
2G5A.00	O/E - Right diabetic foot at risk

2BBW.00	O/E - right eye diabetic maculopathy
2BBX.00	O/E - left eye diabetic maculopathy
2G5B.00	O/E - Left diabetic foot at risk
8HBG.00	Diabetic retinopathy 12 month review
8H7C.00	Refer, diabetic liaison nurse
C109J00	Insulin treated Type 2 diabetes mellitus
66Af.00	Patient diabetes education review
66A6.00	Last hypo. attack
ZLA2500	Seen by diabetic liaison nurse
8Hj0.00	Referral to diabetes structured education programme
7276.00	Pan retinal photocoagulation for diabetes
C10FL00	Type 2 diabetes mellitus with persistent proteinuria
8Hl1.00	Referral for diabetic retinopathy screening
68AB.00	Diabetic digital retinopathy screening offered
8Hj4.00	Referral to DESMOND diabetes structured education programme
F420200	Preproliferative diabetic retinopathy
C104.11	Diabetic nephropathy
8HTk.00	Referral to diabetic eye clinic
9h4..00	Exception reporting: diabetes quality indicators
C100.00	Diabetes mellitus with no mention of complication
2BBL.00	O/E - diabetic maculopathy present both eyes
66AM.00	Diabetic - follow-up default
9N2i.00	Seen by diabetic liaison nurse
C10F.11	Type II diabetes mellitus
M271200	Mixed diabetic ulcer - foot

2BBR.00	O/E - right eye preproliferative diabetic retinopathy
66Ae.00	HbA1c target
2BBS.00	O/E - left eye preproliferative diabetic retinopathy
8H7f.00	Referral to diabetes nurse
42c..00	HbA1 - diabetic control
M271000	Ischaemic ulcer diabetic foot
679R.00	Patient offered diabetes structured education programme
F171100	Autonomic neuropathy due to diabetes
66Am.00	Insulin dose changed
ZL62500	Referral to diabetes nurse
C109700	Non-insulin dependent diabetes mellitus - poor control
F464000	Diabetic cataract
F420z00	Diabetic retinopathy NOS
C10FC00	Type 2 diabetes mellitus with nephropathy
C105.00	Diabetes mellitus with ophthalmic manifestation
8Hj5.00	Referral to XPERT diabetes structured education programme
2BBT.00	O/E - right eye proliferative diabetic retinopathy
C10F600	Type 2 diabetes mellitus with retinopathy
M271100	Neuropathic diabetic ulcer - foot
8Hl4.00	Referral to community diabetes specialist nurse
2BBV.00	O/E - left eye proliferative diabetic retinopathy
C104.00	Diabetes mellitus with renal manifestation
9N0m.00	Seen in diabetic nurse consultant clinic
9OLB.00	Attended diabetes structured education programme
9NN9.00	Under care of diabetes specialist nurse

66Aa.00	Diabetic diet - poor compliance
C107.00	Diabetes mellitus with peripheral circulatory disorder
F372.00	Polyneuropathy in diabetes
66AJz00	Diabetic - poor control NOS
9N2d.00	Seen by diabetologist
8H2J.00	Admit diabetic emergency
2BBF.00	Retinal abnormality - diabetes related
9OL2.00	Refuses diabetes monitoring
66Ad.00	Hypoglycaemic attack requiring 3rd party assistance
8A13.00	Diabetic stabilisation
C10F700	Type 2 diabetes mellitus - poor control
9N0n.00	Seen in community diabetes specialist clinic
93C4.00	Patient consent given for addition to diabetic register
66AJ.11	Unstable diabetes
9M00.00	Informed consent for diabetes national audit
F420300	Advanced diabetic maculopathy
C10F900	Type 2 diabetes mellitus without complication
66AJ000	Chronic hyperglycaemia
66AK.00	Diabetic - cooperative patient
2G5C.00	Foot abnormality - diabetes related
66Ap.00	Insulin treatment initiated
9N0o.00	Seen in community diabetic specialist nurse clinic
9NN8.00	Under care of diabetologist
ZL62600	Referral to diabetic liaison nurse
C100z00	Diabetes mellitus NOS with no mention of complication

N030100	Diabetic Charcot arthropathy
F381311	Diabetic amyotrophy
TJ23A00	Adverse reaction to metformin hydrochloride
M037200	Cellulitis in diabetic foot
C10FN00	Type 2 diabetes mellitus with ketoacidosis
66AN.00	Date diabetic treatment start
8HHy.00	Referral to diabetic register
2G5H.00	O/E - Right diabetic foot - ulcerated
2G51000	Foot abnormality - diabetes related
2G5L.00	O/E - Left diabetic foot - ulcerated
66Ak.00	Diabetic monitoring - lower risk albumin excretion
9OLM.00	Diabetes structured education programme declined
8CR2.00	Diabetes clinical management plan
C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
66A7100	Frequency of GP or paramedic treated hypoglycaemia
ZV65312	[V]Dietary counselling in diabetes mellitus
C103.00	Diabetes mellitus with ketoacidotic coma
ZRB6.00	Diabetes wellbeing questionnaire
66AJ200	Loss of hypoglycaemic warning
9OLK.00	DESMOND diabetes structured education programme completed
C104z00	Diabetes mellitus with nephropathy NOS
F372100	Chronic painful diabetic neuropathy
F3y0.00	Diabetic mononeuropathy
C107.11	Diabetes mellitus with gangrene
F372.11	Diabetic polyneuropathy

66AL.00	Diabetic-uncooperative patient
9kL..00	Insulin initiation - enhanced services administration
9OLL.00	XPERT diabetes structured education programme completed
C109400	Non-insulin dependent diabetes mellitus with ulcer
C10D.00	Diabetes mellitus autosomal dominant type 2
M21yC00	Insulin lipohypertrophy
L180500	Pre-existing diabetes mellitus, insulin-dependent
C109900	Non-insulin-dependent diabetes mellitus without complication
66A7000	Frequency of hospital treated hypoglycaemia
8H4e.00	Referral to diabetes special interest general practitioner
C106z00	Diabetes mellitus NOS with neurological manifestation
C102.00	Diabetes mellitus with hyperosmolar coma
K01x100	Nephrotic syndrome in diabetes mellitus
66AJ300	Recurrent severe hypos
C101z00	Diabetes mellitus NOS with ketoacidosis
G73y000	Diabetic peripheral angiopathy
66Al.00	Diabetic monitoring - higher risk albumin excretion
ZRbH.00	Perceived control of insulin-dependent diabetes
N030000	Diabetic cheiroarthropathy
8A12.00	Diabetic crisis monitoring
C105z00	Diabetes mellitus NOS with ophthalmic manifestation
9OLN.00	Diabetes monitor invitation by SMS (short message service)
8HBH.00	Diabetic retinopathy 6 month review
ZL22500	Under care of diabetic liaison nurse
9OLF.00	Diabetes structured education programme completed

F35z000	Diabetic mononeuritis NOS
8H3O.00	Non-urgent diabetic admission
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
C10G.00	Secondary pancreatic diabetes mellitus
C10F000	Type 2 diabetes mellitus with renal complications
C10F911	Type II diabetes mellitus without complication
C106100	Diabetes mellitus, adult onset, + neurological manifestation
C10FB00	Type 2 diabetes mellitus with polyneuropathy
C10F200	Type 2 diabetes mellitus with neurological complications
7L10000	Continuous subcutaneous infusion of insulin
66AG.00	Diabetic drug side effects
8HLE.00	Diabetology D.V. done
C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
F372200	Asymptomatic diabetic neuropathy
9OLG.00	Attended XPERT diabetes structured education programme
C109600	Non-insulin-dependent diabetes mellitus with retinopathy
U60231C	[X] Adverse reaction to metformin hydrochloride
8Hg4.00	Discharged from care of diabetes specialist nurse
F420500	Advanced diabetic retinal disease
9OL9.00	Diabetes monitoring deleted
M21yC11	Insulin site lipohypertrophy
C10FE00	Type 2 diabetes mellitus with diabetic cataract
2BBk.00	O/E - right eye stable treated prolif diabetic retinopathy
F372000	Acute painful diabetic neuropathy
66AO.00	Date diabetic treatment stopp.

TJ23400	Adverse reaction to gliclazide
8I3k.00	Insulin therapy declined
C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
Cyu2.00	[X]Diabetes mellitus
9OLJ.00	DAFNE diabetes structured education programme completed
C107.12	Diabetes with gangrene
C10zz00	Diabetes mellitus NOS with unspecified complication
44V3.00	Glucose tol. test diabetic
C10F400	Type 2 diabetes mellitus with ulcer
C10FJ11	Insulin treated Type II diabetes mellitus
42WZ.00	Hb. A1C - diabetic control NOS
ZLD7500	Discharge by diabetic liaison nurse
C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
C10K.00	Type A insulin resistance
C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
ZV6DA00	[V]Admitted for commencement of insulin
C101000	Diabetes mellitus, juvenile type, with ketoacidosis
2BBl.00	O/E - left eye stable treated prolif diabetic retinopathy
9OLH.00	Attended DAFNE diabetes structured education programme
C106.13	Diabetes mellitus with polyneuropathy
R054200	[D]Gangrene of toe in diabetic
C10y.00	Diabetes mellitus with other specified manifestation
C10F711	Type II diabetes mellitus - poor control
C10FL11	Type II diabetes mellitus with persistent proteinuria
U602300	[X]Insul/oral hypoglyc drugs caus adverse eff therapeut use

C10z.00	Diabetes mellitus with unspecified complication
C109C00	Non-insulin dependent diabetes mellitus with nephropathy
C10F100	Type 2 diabetes mellitus with ophthalmic complications
679L000	Education in self management of diabetes
C10z100	Diabetes mellitus, adult onset, + unspecified complication
C10FR00	Type 2 diabetes mellitus with gastroparesis
8Hj3.00	Referral to DAFNE diabetes structured education programme
C10FA00	Type 2 diabetes mellitus with mononeuropathy
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
2G5W.00	O/E - left chronic diabetic foot ulcer
F440700	Diabetic iritis
ZC2CA00	Dietary advice for type II diabetes
C10A.00	Malnutrition-related diabetes mellitus
C10N.00	Secondary diabetes mellitus
R054300	[D]Widespread diabetic foot gangrene
C104100	Diabetes mellitus, adult onset, with renal manifestation
C10N100	Cystic fibrosis related diabetes mellitus
F345000	Diabetic mononeuritis multiplex
C109711	Type II diabetes mellitus - poor control
C107200	Diabetes mellitus, adult with gangrene
C10F500	Type 2 diabetes mellitus with gangrene
2BBo.00	O/E - sight threatening diabetic retinopathy
C101100	Diabetes mellitus, adult onset, with ketoacidosis
C109712	Type 2 diabetes mellitus - poor control
C107100	Diabetes mellitus, adult, + peripheral circulatory disorder

8HVU.00	Private referral to diabetologist
C109J12	Insulin treated Type II diabetes mellitus
F381300	Myasthenic syndrome due to diabetic amyotrophy
ZV6DB00	[V]Admitted for conversion to insulin
8HTi.00	Referral to multidisciplinary diabetic clinic
66Ae000	HbA1c target level - IFCC standardised
TJ23000	Adverse reaction to insulins
F420700	High risk proliferative diabetic retinopathy
C10F611	Type II diabetes mellitus with retinopathy
2G5V.00	O/E - right chronic diabetic foot ulcer
C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
F420800	High risk non proliferative diabetic retinopathy
C107400	NIDDM with peripheral circulatory disorder
C10F300	Type 2 diabetes mellitus with multiple complications
8CP2.00	Transition of diabetes care options discussed
N030011	Diabetic cheiropathy
66At.00	Diabetic dietary review
C10M.00	Lipoatrophic diabetes mellitus
9M10.00	Informed dissent for diabetes national audit
C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
C109611	Type II diabetes mellitus with retinopathy
C10FG00	Type 2 diabetes mellitus with arthropathy
C109J11	Insulin treated non-insulin dependent diabetes mellitus

C101y00	Other specified diabetes mellitus with ketoacidosis
C109411	Type II diabetes mellitus with ulcer
8I2S.00	Glitazones contraindicated
C109000	Non-insulin-dependent diabetes mellitus with renal comps
C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
C106y00	Other specified diabetes mellitus with neurological comps
TJ23.00	Adverse reaction to insulins and antidiabetic agents
9h43.00	Excepted from diabetes qual indicators: service unavailable
C106.11	Diabetic amyotrophy
TJ23z00	Adverse reaction to insulins and antidiabetic agents NOS
C104y00	Other specified diabetes mellitus with renal complications
C109612	Type 2 diabetes mellitus with retinopathy
C109212	Type 2 diabetes mellitus with neurological complications
C109200	Non-insulin-dependent diabetes mellitus with neuro comps
C106000	Diabetes mellitus, juvenile, + neurological manifestation
ZRB4.00	Diabetes clinic satisfaction questionnaire
C109412	Type 2 diabetes mellitus with ulcer
ZRB5.11	DTSQ - Diabetes treatment satisfaction questionnaire
C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
8I2P.00	Sulphonylureas contraindicated
C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
C109E11	Type II diabetes mellitus with diabetic cataract
8HKE.00	Diabetology D.V. requested
C10yz00	Diabetes mellitus NOS with other specified manifestation
C109C12	Type 2 diabetes mellitus with nephropathy

C109500	Non-insulin dependent diabetes mellitus with gangrene
C109H00	Non-insulin dependent d m with neuropathic arthropathy
C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
C109011	Type II diabetes mellitus with renal complications
C109300	Non-insulin-dependent diabetes mellitus with multiple comps
U602312	[X] Adverse reaction to insulins
C10zy00	Other specified diabetes mellitus with unspecified comps
U602311	[X] Adverse reaction to insulins and antidiabetic agents
TJ23500	Adverse reaction to glipizide
66Ar.00	Insulin treatment stopped
C109H11	Type II diabetes mellitus with neuropathic arthropathy
889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
9NiC.00	Did not attend DAFNE diabetes structured education programme
66AQ100	Declined consent for diabetes year of care programme
C10yy00	Other specified diabetes mellitus with other spec comps
C10F311	Type II diabetes mellitus with multiple complications
C109E12	Type 2 diabetes mellitus with diabetic cataract
C108y00	Other specified diabetes mellitus with multiple comps
TJ23300	Adverse reaction to glibenclamide
C109511	Type II diabetes mellitus with gangrene
C10y100	Diabetes mellitus, adult, + other specified manifestation
C10N000	Secondary diabetes mellitus without complication
66As.00	Diabetic on subcutaneous treatment
66At100	Type II diabetic dietary review

C109012	Type 2 diabetes mellitus with renal complications
C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
U602316	[X] Adverse reaction to gliclazide
C102z00	Diabetes mellitus NOS with hyperosmolar coma
C109512	Type 2 diabetes mellitus with gangrene
C109F00	Non-insulin-dependent d m with peripheral angiopath
C109C11	Type II diabetes mellitus with nephropathy
C103z00	Diabetes mellitus NOS with ketoacidotic coma
9N1o.00	Seen in multidisciplinary diabetic clinic
C109G00	Non-insulin dependent diabetes mellitus with arthropathy
C105y00	Other specified diabetes mellitus with ophthalmic complicatn
C109F11	Type II diabetes mellitus with peripheral angiopathy
C10FM11	Type II diabetes mellitus with persistent microalbuminuria
C10F411	Type II diabetes mellitus with ulcer
66Au.00	Diabetic erectile dysfunction review
66Av.00	Diabetic assessment of erectile dysfunction
Cyu2000	[X]Other specified diabetes mellitus
C109B11	Type II diabetes mellitus with polyneuropathy
C10F011	Type II diabetes mellitus with renal complications
C103y00	Other specified diabetes mellitus with coma
C109211	Type II diabetes mellitus with neurological complications
ZRB4.11	CSQ - Diabetes clinic satisfaction questionnaire
3883.00	Diabetes treatment satisfaction questionnaire
8IAs.00	Diabetic dietary review declined
2BBr.00	Impaired vision due to diabetic retinopathy

TJ23900	Adverse reaction to tolbutamide
C10FB11	Type II diabetes mellitus with polyneuropathy
C109D11	Type II diabetes mellitus with hypoglycaemic coma
C109111	Type II diabetes mellitus with ophthalmic complications
C109F12	Type 2 diabetes mellitus with peripheral angiopathy
C10A000	Malnutrition-related diabetes mellitus with coma
C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
8HME.00	Listed for Diabetology admissn
C10FA11	Type II diabetes mellitus with mononeuropathy
U60231B	[X] Adverse reaction to tolbutamide
U60231E	[X] Adverse reaction to insulins and antidiabetic agents NOS
Cyu2300	[X]Unspecified diabetes mellitus with renal complications
8HgC.00	Discharged from diabetes shared care programme
66AQ000	Unsuitable for diabetes year of care programme
C10F111	Type II diabetes mellitus with ophthalmic complications
TJ23B00	Adverse reaction to glucagon
C109G11	Type II diabetes mellitus with arthropathy
U602315	[X] Adverse reaction to glibenclamide
C109G12	Type 2 diabetes mellitus with arthropathy
C109A11	Type II diabetes mellitus with mononeuropathy
C10K000	Type A insulin resistance without complication
U60231A	[X] Adverse reaction to tolazamide
C108z00	Unspecified diabetes mellitus with multiple complications
C109112	Type 2 diabetes mellitus with ophthalmic complications

U602318	[X] Adverse reaction to gliquidone
TJ23200	Adverse reaction to chlorpropamide
C10FE11	Type II diabetes mellitus with diabetic cataract
U602317	[X] Adverse reaction to glipzide
C10G000	Secondary pancreatic diabetes mellitus without complication
ZRB6.11	DWBQ - Diabetes wellbeing questionnaire
C10F211	Type II diabetes mellitus with neurological complications
C10E512	Insulin dependent diabetes mellitus with ulcer
C10FD11	Type II diabetes mellitus with hypoglycaemic coma
SL23100	Biguanide poisoning
Kyu0300	[X]Glomerular disorders in diabetes mellitus
C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn
C10FC11	Type II diabetes mellitus with nephropathy
66Aw.00	Insulin dose
TJ23800	Adverse reaction to tolazamide