Redacted study protocol

Incidence of Thyroid Neoplasm and Pancreatic Cancer in Type 2 Diabetes Mellitus Patients who Initiate Once Weekly Exenatide Compared with Other Antihyperglycemic Drugs

Redacted protocol based on original protocol version 3 of August 14, 2013

LAY SUMMARY

Many patients with diabetes mellitus, increased sugar levels, are treated with medicines. Different types of medicines are available. The present study is intended to monitor the occurrence of two types of cancer with weekly exenatide. Anonymised electronic health care records will be used to monitor the weekly exenatide users and compare them to patients using other types of medication.

1 BACKGROUND

Diabetes mellitus is a major public health problem worldwide and especially in the United Kingdom (UK). According to Diabetes UK, approximately 2.8 million people in the UK had diabetes in 2010 [1]. Type 2 diabetes (T2DM) accounts for 90-95% of diagnosed cases of diabetes and is associated with older age, obesity, family history of diabetes, gestational diabetes, impaired glucose metabolism, physical inactivity. Diabetes is a leading cause of blindness, end-stage renal disease, non-traumatic lower limb amputation, and is a major risk factor for coronary artery disease and stroke [2]. Interventions that improve glycemic control reduce microvascular complications involving the eyes, kidneys and nerves, and may reduce macrovascular complications such as myocardial infarction [3].

Many of the traditional diabetes medications (such as sulfonylureas (SU), metformin, α-glucosidase inhibitors, thiazolidinediones (TZDs), and insulin) lower blood glucose, but they may also produce hypoglycemia, gastrointestinal symptoms, or weight gain. The American Diabetes Association recommends a hemoglobin A1C goal of less than 7%, but many diabetic patients are unable to achieve this goal by using oral drug combinations or diet and exercise. Most patients with T2DM will eventually require combination therapy to maintain glycemic control. Several newer treatments have been developed that provide valuable alternatives to improve long-term glycemic control for T2DM [4]. Exenatide, an incretin-mimetic, is one of the newer treatment alternatives available (initially approved by the Food and Drug Administration on 28 April 2005). Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist that enhances glucose-dependent insulin secretion by pancreatic beta cells, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying.

Review of recent data on the newer antidiabetic agents has noted signals of pancreatitis and pancreatic and thyroid malignancies with GLP-1 drugs. Acute pancreatitis has been reported as a rare adverse effect of exenatide therapy principally in suspected adverse drug reaction reports, however, this increased association was not supported by recent pharmacoepidemiologic studies [5; 6]. In rodent toxicology studies, “C-cell hyperplasia” and C-cell carcinoma (the rodent equivalent of human medullary thyroid cancer (MTC) were detected with the long-acting glucagon like peptide 1 (GLP-1) receptor agonist class (for example, liraglutide and exenatide]). A GLP-1 receptor-mediated mode of action has been proposed with respect to carcinogenicity in the rodent thyroid [7]. It is important to note that in the thyroid of various species, including rodents, monkeys, and humans, GLP-1 receptors are expressed only on C-cells, not on other thyroid cell types [8]. Accordingly, across multiple preclinical studies of all GLP-1 receptor agonists in rodents, which included near-lifetime treatment at relatively high exposure multiples, there was no evidence of an increase in thyroid tumors of cell types other than C-cells.

Data both from clinical studies (approximately 5400 patient-years of exposure in long-term studies) and postmarketing exposure (approximately 1.7 million patient-years) have shown no evidence for an increased risk of thyroid malignancy in general; no case of MTC has been reported with either exenatide formulation (available as daily injection [Byetta] or weekly injection [Bydereon]). Furthermore, in primates, there is no detectable stimulation of calcitonin release by GLP-1 receptor activation. These data provide additional support for a lack of relevance of the rodent C-cell findings to humans.

The current study is being conducted to meet a request made by the European Medicines Agency prior to approving exenatide once weekly for marketing in the European Union.

2 OBJECTIVES

The objective of this study is to estimate and compare the incidence of thyroid neoplasm and pancreatic cancer among initiators of exenatide once weekly compared with users of other oral antidiabetic agents (OADs).

2.1 Primary Objectives:

● To conduct individual medical review of cases of newly diagnosed thyroid or pancreas cancer among initiators of exenatide once weekly
● To estimate the absolute and relative incidence of newly diagnosed thyroid cancer among initiators of exenatide once weekly compared with matched control cohort of other OADs
● To estimate the absolute and relative incidence of newly diagnosed pancreas cancer among initiators of exenatide once weekly compared with matched control cohort of other OADs

2.2 Secondary Objectives:

● Describe the incidence of medullary thyroid cancer (MTC) among initiators of exenatide once weekly and matched control cohort of other OADs
● Estimate the incidence of new-onset benign thyroid neoplasm among initiators of exenatide once weekly compared to a matched control cohort of other OADs
● To conduct individual medical review of cases of newly diagnosed thyroid or pancreas cancer among initiators of exenatide (weekly or daily)
● To estimate the absolute and relative incidence of newly diagnosed thyroid cancer among initiators of exenatide (weekly or daily) compared with matched control cohort of other OADs
● To estimate the absolute and relative incidence of newly diagnosed pancreas cancer among initiators of exenatide (weekly or daily) compared with matched control cohort of other OADs

3 METHODS

3.1 Overview of Study Design

This will be a retrospective cohort study of initiators of exenatide once weekly and matched control cohort of other OAD. The data sources will include the Clinical Practice Research Datalink (CPRD) and the linked Hospital Episode Statistics (HES), death certificates and cancer registry. Exenatide once weekly initiators will be matched to two control cohorts of prevalent OAD users based on age, sex and practice and on propensity scores. This will be a hypothesis testing study.

3.2 Data Sources

The study will be conducted in the Clinical Practice Research Datalink (CPRD) and linked Hospital Episode Statistics (HES), death certificates and Cancer Registry. The CPRD comprises computerized medical records of general practitioners (GPs) including about 12 million patients from 1987 onwards of which approximately 3.6 million are currently active. GPs play a gatekeeper role in the UK health care system, as they are responsible for primary health care and specialist referrals. Patients are semi-permanently affiliated to a practice, which centralizes the medical information from the GPs, specialist referrals and hospitalizations. The data recorded in the CPRD include demographic information,

prescription details, clinical events, preventive care provided, specialist referrals, laboratory results, hospital admissions and death.

Practices that want to contribute data to CPRD are carefully selected and trained in the software used to record medical data. Only those practices that meet quality standards are then used for research (about 10% of the practices that send data to CPRD do not meet the quality standards). Furthermore, validation studies are conducted regularly by comparing CPRD data to written notes of general practitioners. No other UK database restricts the data only to practices providing high quality data or with procedures for measuring and maintaining data quality and with frequent validation studies.

The CPRD currently contains the complete anonymized patient medical records from GPs who agree to adhere to "Recording Guidelines" that are subject to detailed quality control checks of data at both practice and individual patient level. CPRD can now be linked individually and anonymously to other NHS datasets in England (appropriate approvals have been obtained for this; investigators have no access to patient identifiers). Currently, > 300 GP practices in England are participating in this linkage (about 50% of CPRD in the UK and 65% of the practices in England). Data from the following sources will be used for this study (for patients in practices participating in the linkages):

- **CPRD**
- **Hospital Episode Statistics (HES)**. These data contain details of the date, main discharge diagnosis, procedures and duration of hospitalisation, as provided by the hospitals for all admissions to NHS hospitals in England. The patients include private patients and those resident outside of England, who were treated in NHS hospitals, as well as care delivered by treatment centres (including those in the independent sector) funded by the NHS. All NHS trusts in England, including acute hospitals, primary care trusts and mental health trusts are included.
- **ONS Death certificates**. The ONS Death certificate data contains the date and cause of death for England and Wales, along with the primary and secondary causes of death.
- **Cancer registry**. Cancer registration in England is conducted by nine regional registries, which collect and collate data on cancers resident in their area, and submit a standard dataset on these registrations. Malignancies are classified according the International Classification of Diseases 10 (ICD-10).

Recent research has found that the patients from practices that are in the linkages are similar to patients from practices not included in the linkages (data not yet published). The lag time between data entry of an event in the linked dataset and availability for research is currently several months for HES and death certificates but several years for the cancer registry data. This lag time may improve in the future.

Primary data analysis will be performed using CPRD data. Cancer registry data will be used to identify MTC cases for the descriptive analyses portion of the study.

3.3 Study Population

The study cohort will consist of adults aged 18 years and older with a diagnosis of diabetes mellitus as recorded in the medical record. Patients with a record of type I diabetes will be excluded. Two exenatide cohorts will be created. The first cohort of incident weekly exenatide users will include patients with a first-ever prescription for weekly exenatide after July 2011 (launch date of weekly exenatide) and with at least one year of enrollment in CPRD prior to this prescription. The index date of the exenatide cohort will be the date of the first weekly exenatide prescription. Patients who start exenatide once weekly but have a history of prior prescribing of exenatide daily will be excluded. The second exenatide cohort will include weekly and daily exenatide users with an index date of the first-ever exenatide prescription after January 2007 (launch date of daily exenatide).The main interest for the risk management of weekly exenatide will be the analyses of the first exenatide cohort.

Each exenatide cohort will be matched to one control cohort including prevalent users of other OADs on or after July 2011 (for the matching to the first exenatide cohort) or January 2007 (for the matching to the second exenatide cohort). The control cohort will include patients using OADs other than Incretin drugs; patients who initiate treatment with incretin drugs will be censored at the date of initiation of incertin drugs. The index date of the control cohort will be the first prescription of other OADs after July 2011/January 2007 with at least one year of enrollment in CPRD prior. The inception cohort approach for exenatide is considered the preferred approach for evaluating the effects of cumulative exposure over time. The medication of interest in this study will be exenatide once weekly. Patients with a history of cancer (any type except non-melanoma skin cancer) prior to the index date will be excluded. Patients will be followed from the index date up to the occurrence of the cancer of interest or the end of data collection (i.e., last CPRD data collection, transfer out of the practice or date of death, whichever date came first). Patients in the control cohort will also be censored at the first prescription of exenatide.

3.4 Outcome Identification

The primary outcomes will be incident thyroid neoplasm and pancreas cancer. Outcomes recorded in CPRD, HES, death certificates and cancer registries will be analyzed separately. Secondary outcomes will include benign thyroid neoplasm and MTC. The Read codes for identification of pancreatic cancer and thyroid neoplasm are listed in Table 1.

3.5 Matching of controls to the exenatide cohorts

For each of the two exenatide cohorts, we will create two matched control cohorts. The first matched control cohort will be based on randomly selecting six OAD patients on the basis of age, sex and practice. The age matching will be done in a stepwise manner by year of age up to a maximum difference of five years. If six controls can not be found for a weekly exenatide initiator within the same practice, the remaining controls will be randomly selected from other practices (matching by age in a stepwise manner). The second control cohort will be based on matching by propensity score with the aim of achieving balance between comparison groups in terms of all identified predictors of weekly exenatide initiation. Propensity-score matching produces groups that have similar patterns of the presence or absence of a large number of factors. The propensity score method can incorporate dozens of predictors of the choice of one therapy over another (such as past drug utilization, past hospitalizations, current comorbidities, age, sex, geographic region, and calendar time). For a given covariate pattern, the propensity score is the fitted value of the probability of being a member of the exenatide cohort, given membership in the study population and the covariate pattern.

We will develop propensity scores for exenatide initiation using the information derived from the baseline characterization of exenatide initiators (Section 3.6). The propensity score will be modeled using an unconditional logistic regression model incorporating the predictors of exenatide initiation. First, a set of variables will be identified based on univariate c-statistics and clinical importance to be forced into the model. Second, we will include time indicators (calendar year), and assess for interactions between calendar year and the ten variables most predictive of exenatide initiation (based on univariate c-statistic) to accommodate changes in the way that antidiabetic drugs are used over time. Third, the propensity score will be modeled incorporating the forced into variables, the significant interaction terms ($p<0.1$), and the remaining predictors of exenatide initiation using a stepwise selection to retain no more than 1/10th as many variables as exenatide initiators. Each subject will be assigned a propensity score, and each exenatide initiator will be matched to 6 OAD initiators using a greedy matching algorithm. The groups matched by propensity score will have comparable marginal distributions of the baseline characteristics, but it does not mean that subjects will be individually matched on each factor that will go into creating the propensity score. We will compare the selected covariates during the baseline period between matched

groups and identify any unbalanced covariates after matching. These unbalanced covariates will be added in the final models estimating the risk of pancreatic or thyroid cancer associated with exenatide exposure to mitigate the residual confounding resulting from the unbalanced matching.

We will evaluate whether the matching process removes patients from the matched cohorts with extreme propensity scores. If exenatide-exposed patients with extremely low propensity scores, or OAD-exposed patients with extremely high propensity scores remain in the matched cohorts, we will "trim" extreme values of the propensity score distributions in order to exclude subjects who are not candidates for exenatide use or who are absolute candidates for exenatide use. The expected benefit of "trimming" is that the exclusion of these patients will mitigate the impact of unmeasured confounding [10]. We will describe the characteristics of the exenatide patients for whom we are unable to find suitable matches.

3.6 Covariates

Covariates derived will be defined for a broad range of characteristics including demographics, diagnosis, medical procedures, drug use, and health care utilization as measured on the index date. At a minimum, we will describe the exenatide and comparator cohorts with respect to the following:

Demographics:
(i) Age, sex, race (where available)
(ii) Geographic area
(iii) Calendar year of index date

Diabetes severity indicators:
(i) Use of OAD medications by type and insulin in the one year before
(ii) Duration of diabetes (as defined by the first-ever record of either a medical code for diabetes or a prescription for diabetes medication)
(iii) Peripheral neuropathy ever before
(iv) Nephropathy ever before
(v) Retinopathy ever before
(vii) HbA1C measurements (most recent measurement in the six months before index date)

Cardiovascular disease indicators:
(i) Treated hypertension (i.e., history of hypertension ever before and prescribing of antihypertensives in the one year before)
(ii) Hyperlipidemia ever before
(iii) Hypertriglyceridemia ever before
(iv) Ischemic heart disease ever before
(v) Myocardial infarction ever before
(vi) Congestive heart failure ever before
(vii) Stroke ever before

Other:
(i) Alcohol use
(ii) Smoking
(iii) Body mass index
(iv) small-area socioeconomic status (for linked practices)
(v) Hospitalization in the one year before
(vi) number of different drugs dispensed in the one year before
(vii) number of laboratory tests performed

(viii) Evidence of pancreatic disease and thyroid disease ever before
(ix) history of gall bladder disease ever before
(x) symptom of liver enlargement or record of fatty liver ever before
(xi) number of lipid-lowering drugs in the one year before the index date

In case of missing information (such as body mass index, smoking and alcohol history), indicators of missingness will be used in the regression analyses. We will not use multiple imputation as previous CPRD has found that non-recording of information may not be random (conditional on the risk factors in the imputation model).

4 ANALYSIS

This section outlines the principles of the planned analysis. Additional information and shell tables will be included in the statistical analysis plan.

Starting 2 years post-marketing of exenatide once weekly in the UK, CPRD will perform annual descriptive analyses of all cases of thyroid and pancreas cancer in the CPRD (Section 4.1. 4.2, 4.3). This will include a medical review of cases of incident thyroid or pancreas cancer. The second part of the analysis (sections 4.4 to 4.7) will be conducted when the number of weekly exenatide users exceeds 20,000.

4.1 Description of Baseline Characteristics

Baseline characteristics including demographics, medical history and prescription drug history, and health care services will be tabulated for initiators of exenatide and the control OAD cohorts.

4.2 Medical review of cases of incident thyroid or pancreas cancer

All cases of incident thyroid or pancreas cancer in the exenatide cohorts will be identified and a random sample (of a similar number) of incident cases will be drawn from the control cohorts. All available information from the medical and prescriptions will be extracted and details on the name of the diabetes drugs will be replaced by a blinded indicator of class of diabetes medication (class A, B, C etc). Two medical reviewers will review these cases and conduct a causality assessment. Any discrepancy in this assessment will be noted.

4.3 Annual Descriptive Analyses on incidence rates of Thyroid and Pancreas Cancer

This analysis will be purely descriptive with no formal statistical hypothesis testing. Crude incidence rates (with 95% confidence intervals) will be estimated and provided until the formal statistical analyses are conducted.

4.4 Analysis of propensity matching

In order to provide reassurance that any non-significant results are not due to low power of the study caused by unnecessary exclusion of subjects, and that true effects have not been underestimated, the following sensitivity analyses and data displays will be conducted:

a) A breakdown of the inclusion criteria failed by the complete patient population split by exposure group.

b) An analysis of the age-sex matched cohorts, adjusting for propensity score for all subjects in the cohort, regardless of DPP-4 inhibitors/GLP-1 receptor agonists use.

c) An analysis of the age-sex matched cohorts, adjusting for propensity score with censoring at first prescribing of DPP-4 inhibitors/GLP-1 receptor agonists use.

d) The distribution of propensity scores for once weekly exenatide users and control cohort.

f) An analysis looking at the relative risk per decile of the propensity score.

4.5 Bias analysis

This analysis will evaluate the possible extent of bias in the comparisons between different diabetes medications and whether statistical adjustment with risk factors would sufficiently address any confounding. In this analysis, the cancer incidences during the 12 months after the index date will be compared between the different cohorts. The first year after drug initiation will be used as lag period. Given that any causal effects of treatment are unlikely to be observed in the first 12 months of use, increased relative rates could indicate residual confounding (i.e., effects of the underlying disease).

4.6 Intent-to-treat Analysis

We will compare the occurrence of the outcomes of interest in the inception cohorts of exenatide with the OAD control cohorts. We will conduct an "intent-to-treat" or "as-matched" analysis that holds the original exposure assignment constant from the date of accrual through the end of follow-up. Person-time will be calculated from the index date until the earliest occurrence of the outcome of interest, loss to follow-up, or last date of data collection. The outcomes of interest will be analyzed separately. Incidence rates of each type of treatment-emergent neoplasm will be estimated for the exenatide and the OAD comparator cohorts, in totality and by subtypes of thyroid neoplasm. Incidence rates will also be presented by class of OADs and by duration of follow-up (in one-year increments). This categorization with respect to length of follow-up will provide evidence about the relevant etiologic timing of exenatide exposure with respect to the neoplasm outcomes under study. Kaplan-Meier plots will be used to depict the cumulative probability of the neoplasm outcomes of interest. Cox proportional hazards regression models will be used to estimate the relative hazards of treatment-emergent pancreatic cancer and thyroid neoplasm with appropriate 95% confidence intervals.

4.6 Time-dependent Analysis

An additional analysis will classify the follow-up period into periods of current and past exposure. Current exposure will be the time from the date of a prescription up to six months or the date of the next prescription, whichever came first. Duration of current exposure will be analyzed. Past exposure will be defined as the time from 6 months after a prescription up to end of data collection. Time-dependent Cox regression will be used.

4.7 Patterns of risk

The patterns of cancer incidence over time within each cohort will also be evaluated. Poisson regression analysis will be used to compare the incidence during the first 12 months of follow-up to those during 12-24, 25-60 and 60+ months. In addition to providing the results of these statistical models (that rely on categorizing follow-up time into a few groups), the patterns of risks over time will be visualized. Follow-up will be divided into 100 periods in order to estimate the incidence rate within smaller periods of time and the absolute risk will be estimated within each small period. These estimates will then be smoothed using the methods proposed by Ramlau-Hansen.

5 SAMPLE SIZE AND POWER ESTIMATES

Sample sizes were calculated for a test for differences in two exponential survivor functions with an assumed hazard rate of 3.2 per 100,000 years [11] among the control group and a sample size ratio of 1 weekly exenatide users to 6 control patients. Sample sizes were calculated to detect a hazard ratio of 1.5, 2.0, 3.0 or 4.0 for varying follow-up periods and proportions of loss to follow-up (NB. the rate of loss to follow up in the period was assumed to be similar in both groups).

HR	Years of follow-up	%loss to FU		Sample size			Significance level (2-sided)	Power
		Control	Exposed	Total	Control	Exposed		
1.5	1	0%	0%	9,401,343	8,058,291	1,343,052	0.05	0.8
1.5	1	20%	20%	10,489,238	8,990,772	1,498,466	0.05	0.8
1.5	1	30%	30%	11,177,399	9,580,624	1,596,775	0.05	0.8
1.5	5	0%	0%	1,880,413	1,611,782	268,631	0.05	0.8
1.5	5	20%	20%	3,120,498	2,674,711	445,787	0.05	0.8
1.5	5	30%	30%	4,030,856	3,455,018	575,838	0.05	0.8
2.0	1	0%	0%	2,682,815	2,299,555	383,260	0.05	0.8
2.0	1	20%	20%	2,993,262	2,565,652	427,610	0.05	0.8
2.0	1	30%	30%	3,189,639	2,733,975	455,664	0.05	0.8
2.0	5	0%	0%	536,612	459,953	76,659	0.05	0.8
2.0	5	20%	20%	890,491	763,277	127,214	0.05	0.8
2.0	5	30%	30%	1,150,276	985,950	164,326	0.05	0.8
3.0	1	0%	0%	831,025	712,306	118,719	0.05	0.8
3.0	1	20%	20%	927,188	794,732	132,456	0.05	0.8
3.0	1	30%	30%	988,017	846,871	141,146	0.05	0.8
3.0	5	0%	0%	166,226	142,479	23,747	0.05	0.8
3.0	5	20%	20%	275,844	236,437	39,407	0.05	0.8
3.0	5	30%	30%	356,315	305,412	50,903	0.05	0.8
4.0	1	0%	0%	438,676	376,007	62,669	0.05	0.8
4.0	1	20%	20%	489,437	419,517	69,920	0.05	0.8
4.0	1	30%	30%	521,547	447,040	74,507	0.05	0.8
4.0	5	0%	0%	87,749	75,213	12,536	0.05	0.8
4.0	5	20%	20%	145,615	124,812	20,803	0.05	0.8
4.0	5	30%	30%	188,093	161,222	26,871	0.05	0.8

6 LIMITATIONS

There are various strengths and limitations to this study. This study will be based on an analysis of electronic medical records. While electronic medical records data are extremely valuable for the efficient and effective examination of health care outcomes, treatment patterns, health care resource utilization, and costs, certain inherent limitations need to be taken into consideration. Presence of a drug in the database does not indicate that the medication was consumed or that it was taken as prescribed. Medications filled OTC, prescribed in the hospital or by specialists or provided as samples by the physician will not be observed in CPRD. Because cancer outcomes tend to have long latency periods, we will categorize person-time according to length of follow-up. Person-time that occurs later in follow-up is more likely to give rise to pancreatic and thyroid cancer for which the study drug exposure occurred during a relevant etiologic period, allowing empirical assessment of the latency period of the outcomes.

The study will include cancer outcomes obtained through three independently collected databases, including cancer registry data. But the information on confounders and underlying disease severity will be limited in this study. Furthermore, our analyses will provide only simplistic representations of the actual exposures to diabetes medications. Drug exposure in actual clinical practice often varies greatly, with many different drug combinations being used and patients switching over time between drugs and patients being non-compliant to treatment instructions. We will also rely on information of prescriptions rather than actual use. We expect to see similar challenges assessing a causal association with exenatide and cancer as those seen with prior studies assessing the association between insulin use/diabetes and cancer. These include issues of allocation bias and inability to control for confounding factors; making it difficult to discern if the association is due to the severity of diabetes and/or patient characteristics rather than a true effect of the anti-diabetic agent.

Vigneri outlined the challenges in this field of research: *"The complexity of the various diabetic conditions, the diversities in the biology of different forms of cancer and the multiplicity of the possible mechanisms involved, prevent a comprehensive and definite answer to many questions regarding the association of diabetes* [or diabetic therapy] *with an increased risk of cancer initiation and progression. Most epidemiologic studies have not carefully considered* [or unable to consider] *a series of confounding factors and diabetic patients have not been adequately characterized for the type of diabetes, the duration of the disease, the drugs used for therapy, the quality of the metabolic control and the presence of co-morbidities. Because of the intrinsic heterogeneity of both diabetes and cancer, studies on the association of the two diseases are not easy to carry out. Indeed, considering the wide array of possible mechanisms causing increased cancer incidence and mortality in diabetic patients, it is difficult to accurately define the aims, the recruitment criteria and the appropriate design for such studies (Vigneri 2009)."*

A recent CPRD of the effects of diabetes medication on cancer risk found that there was a substantial bias and confounding in the direct comparisons between the different diabetes medications and that statistical adjustment only marginally reduced confounding [12]. Propensity matching will rely on an assumption of completeness of recording of reasons for initiating a treatment. This assumption may not be correct and residual confounding may remain.

An important limitation is the limited statistical power of this study. However, it is considered prudent to conduct a study that may be underpowered statistically rather than not conducting a study. The study will include clinical review of cases, which could help to detect signals of drug toxicity.

7 STUDY MANAGEMENT

7.1 Deliverables

The deliverables will be as follows:

- Study Protocol (Draft #1, Draft #2, Draft #3, and Final)
- Statistical Analysis Plan (Draft #1, Draft #2, Draft #3, and Final)
- Written Report Summarizing the Results of the Analyses (Draft and Final)

7.2 Timelines

1) Annual descriptive analyses of incident cases of thyroid and pancreas cancer:

a. Annual update (descriptive analysis of incident cases) starting two years after once week exenatide was launched in UK (launch date July 2011).

2) **Formal Epidemiological Study assessing Exenatide exposure and Thyroid/Pancreatic Cancer**:

a. Interim analysis when there are 20 000 once week exenatide users in CPRD

b. Final analysis when there are 55 000 once week exenatide users in CPRD

8 PLANS FOR DISSEMINIATING AND COMMUNICATING STUDY RESULTS

We plan to present our findings at scientific meetings and publish the results in a peer-reviewed scientific journal.

9 REFERENCES

1.Diabetes UK. Reports and Statistics: Diabetes Prevalence 2010. Available on the web at: www.diabetes.org.uk

2. Miser W. The Management of Type 2 Diabetes Mellitus FOCUS on Quality. Prim Care Clin Office Pract 2007;34:1-38. 34, 1-38. 2007.

3. Bolen S, Wilson L, Vassy J, Feldman L, Yeh J, Marinopoulos S et al. Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults with Type 2 Diabetes. Comparative Effectiveness Review No I (Prepared by Johns Hopkins Evidence-based Practice Center under Contract No 290-02-0018) Rockville, MD: Agency for Healthcare Research and Quality 2007.

4. LeRoth D, Rayfield E. The benefits of tight glycemic control in type 2 diabetes mellitus. Clinical Cornerstone 2007;8(Suppl 7):S19-S29. 8, S19-S29. 2007.

5. Dore DD, Bloomgren GL, Wenten M, Hoffman C, Clifford CR, Quinn SG et al. A cohort study of acute pancreatitis in relation to exenatide use. Diabetes Obes Metab 2011.

6. Garg R, Chen W, Pendergrass M. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. Diabetes Care 2010; 33(11):2349-2354.

7. Lamari Y, Boissard C, Moukhtar MS, Jullienne A, Rosselin G, Garel JM. Expression of glucagon-like peptide 1 receptor in a murine C cell line: regulation of calcitonin gene by glucagon-like peptide 1. FEBS Lett 1996;393(2-3):248-252.

8. Bjerre Knudsen L, Madsen LW, Andersen S, et al. Glucagon-like Peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. Endocrinology 2010;151(4):1473-1486.

9. Parks M, Rosebraugh C. Weighing risks and benefits of liraglutide--the FDA's review of a new antidiabetic therapy. N Engl J Med 2010; 362(9):774-777.

9. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. JAMA 1995; 273(20):1605-1609.

10. Sturmer T, Rothman KJ, Avorn J, Glynn RJ. Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution--a simulation study. Am J Epidemiol 2010; 172(7):843-854.

11. Cancer Research UK. Thyroid cancer - UK incidence statistics, 2008. Available on the web at: http://info.cancerresearchuk.org/cancerstats/types/thyroid/incidence/

12. van Staa TP, Patel D, Gallagher AM, De Bruin ML, Møller H. Oral antidiabetics and insulin and the patterns of risk of cancer: a study with the General Practice Research Database and secondary care data. Diabetologia 2012;55:654-65.

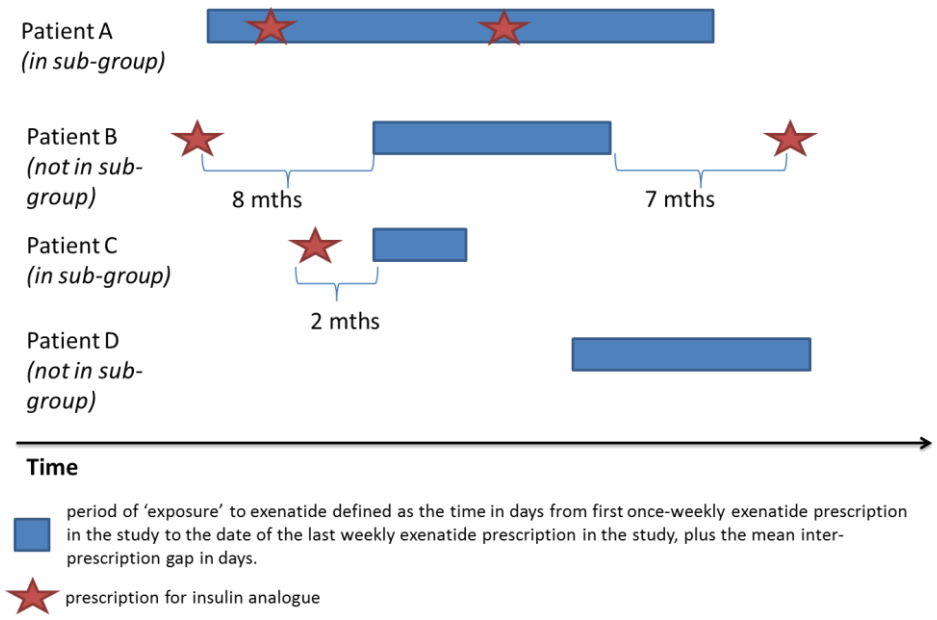
Table 1. **Diagnosis Codes for Identification of Study Outcomes**

Medcode	Readcode	Readterm
Pancreatic Cancer		
63102	BB5B100	[M]Islet cell carcinoma
21659	BB5Bz00	[M]Pancreatic adenoma or carcinoma NOS
8032	BB5B.00	[M]Pancreatic adenomas and carcinomas
16931	B80z000	Carcinoma in situ of pancreas
10949	B162.00	Malignant neoplasm of ampulla of Vater
40810	B171.00	Malignant neoplasm of body of pancreas
96635	B17y000	Malignant neoplasm of ectopic pancreatic tissue
8771	B170.00	Malignant neoplasm of head of pancreas
35795	B174.00	Malignant neoplasm of Islets of Langerhans
48537	B17y.00	Malignant neoplasm of other specified sites of pancreas
8166	B17..00	Malignant neoplasm of pancreas
34388	B17z.00	Malignant neoplasm of pancreas NOS
35535	B173.00	Malignant neoplasm of pancreatic duct
95783	B17yz00	Malignant neoplasm of specified site of pancreas NOS
39870	B172.00	Malignant neoplasm of tail of pancreas
97875	B175.00	Malignant neoplasm, overlapping lesion of pancreas
55675	B717011	Endocrine tumour of pancreas
16828	B905100	Neoplasm of uncertain behaviour of pancreas
Thyroid Neoplasm		
19263	BB5f.00	[M]Thyroid adenoma and adenocarcinoma
38685	BB5fz00	[M]Thyroid adenoma or adenocarcinoma NOS
8958	B8yy000	Carcinoma in situ of thyroid gland
5637	B53..00	Malignant neoplasm of thyroid gland
37758	B7G..00	Benign neoplasm of thyroid gland

Study population:

Of those patients eligible for the study, we will further identify a sub-group of patients who are co-prescribed insulin analogues. Any patient who receives one or more prescriptions for an insulin analogue (e.g. insulin lispro, insulin aspart, insulin glulisine) in the three months prior to initiation of exenatide once-weekly will be included in the sub-group. Additionally, any patient who receives a prescription for an insulin analogue whilst 'exposed' to exenatide will also be included in the sub-group. Here, the period of 'exposure' will be defined as the time in days from first once-weekly exenatide prescription in the study to X days after the last weekly exenatide prescription in the study, where X is the mean inter-prescription gap in days. Our exposure definition is based on prescriptions for exenatide only because of incomplete recording of dosing and prescription quantity data for exenatide in CPRD.

A diagram illustrating patients eligible and not eligible for inclusion in the sub-group is shown below.



Analysis:
All analyses as described under '4. Analysis' will be undertaken on this sub-group, subject to a sufficiently large sample being available to support the respective analyses.

Limitations:
As we are using a crude definition of exposure (based on first and last exenatide prescriptions) to identify co-prescribing with insulin analogues; there is a possibility that we may wrongly place an individual in the sub-cohort if they were prescribed an insulin analogue during a gap in exenatide treatment. For example, if a patient initiated exenatide for 2 months, then received an insulin analogue prescription 6 months later (while they were not on exenatide) and then resumed exenatide after using an insulin analogue, we would consider this person in the sub-cohort using our definition of exposure.