Annual descriptive analysis on the incidence of thyroid neoplasms and pancreatic cancer in type 2 diabetes mellitus patients who initiate once-weekly exenatide

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Introduction

Exenatide is one of the newer treatments available for improving glycaemic control in patients with type 2 diabetes mellitus (T2DM). It is currently available for administration as a once-weekly sub-cutaneous injection (Bydureon – hereafter referred to as 'exenatide once-weekly') or a twice daily sub-cutaneous injection (Byetta – hereafter 'exenatide-daily'). 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.[1] Findings of medullary thyroid cancer in non-clinical studies in rats, as well as post marketing reports of pancreatitis and pancreatic cancer in patients with T2DM, treated with exenatide and other GLP-1 receptor agonists, have warranted additional pharmacoepidemiological assessments. Recent evidence from a meta-analysis of 25 longitudinal studies found insufficient evidence to support an increased risk of cancer with GLP-1 receptor agonist use in patients with T2DM.[2] Further, a drug safety study focusing specifically on exenatide, found no association between dispensing of exenatide-daily and thyroid neoplasms and pancreatic cancer.[3]

The current study provides annual descriptive statistics to support AstraZeneca's post-marketing safety study on the incidence of thyroid neoplasm and pancreatic cancer in patients with T2DM who initiate exenatide once-weekly. The current study forms part of a request made by the European Medicines Agency prior to approving exenatide once-weekly for marketing in the European Union.

Objective

The objectives of the annual descriptive analysis were to:

- describe the baseline characteristics of exenatide once-weekly initiators; and
- estimate incidence rates of thyroid neoplasm and pancreatic cancer among initiators of exenatide once-weekly.

Methods

Information for the study was obtained from the Clinical Practice Research Datalink (CPRD), using their primary care database (GOLD).

GOLD comprises the computerised medical records of general practitioners. General practitioners (GP) play a key 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 centralises the medical information from the GPs, specialist referrals and hospitalisations. Practices that want to contribute data to GOLD 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 contribute data do not meet the quality standards). Furthermore, validation studies are conducted regularly by comparing the electronic data to the written notes of general practitioners. The data recorded in GOLD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes. The database currently includes over 13 million patients from 1987 onwards, of which data is currently being collected on over 5 million. GOLD is a dynamic database where patients can join and leave at any time. This means that the patients involved in a study are likely to change from one month to the next. Care should be taken when comparing results between studies.

Study Design

This was a retrospective cohort study using prospectively recorded primary care data. All code lists in this study were externally reviewed for relevance, accuracy and completeness by the CPRD consultant GP.

Study Period

The study period for the current analysis was from 1st July 2011 to 30th June 2014.

Study Population

The study population consists of patients who initiated exenatide once-weekly. From a starting population of all acceptable[i] patients in GOLD (N=13,583,718), the following criteria were used to define the cohort:

Inclusion Criteria

- Patient with a prescription for exenatide once-weekly (N=1,176)
- Male or female only (N=1,176)
- First (index) prescription for exenatide once-weekly during the study period (N=1,148)
- Index prescription recorded during a patient's up-to-standard (UTS) follow-up (N=1,126)
- Patient aged 18 years or more at the time of index prescription (N=1,126)
- At least one year of prior registration in GOLD before index prescription (N=1,044)
- History of type 2 diabetes mellitus in GOLD on or before initiation of exenatide once-weekly (N=1,024)

Exclusion Criteria

- A record of type 1 diabetes mellitus (T1DM) on or before initiation of exenatide once-weekly (N=992)
- History of any cancer (except non-melanoma skin cancer) prior to index date (N=936)
- Prior prescription of DPP4 inhibitors or other GLP1 products (N=314)
- Prior prescription of exenatide-daily (N=179)

The index date was defined as the date of the first exenatide once-weekly prescription.

Outcomes

The outcomes were incidence thyroid neoplasms (any, benign or malignant) and pancreatic cancer recorded on or after the index date and before the end of follow-up in GOLD. Code lists for the outcomes are available in Annex 3.

[i] See full description in Annex 2.

Statistical analysis

Main Analysis

This analysis was purely descriptive with no formal statistical hypothesis testing. The analysis provides baseline characteristics of exenatide once-weekly initiators and aimed to estimate crude incidence rates for thyroid neoplasm (benign and malignant) and pancreatic cancer.

CPRD research is subject to a number of governance requirements, one of which relates to the reporting of small cell counts. Here, a cell count refers to a single result in a table which counts the number of patients with a particular outcome, co-variate, etc. When the number of patients reported in a single cell is small, there is a potential for unintentional identification of patients. In these situations, the small cell count is suppressed (replaced with a blank or a symbol) to prevent disclosure and protect confidentiality. The standard line on this can be found at: http://www.cprd.com/ISAC/governance.asp, under 'Reporting of the findings':

> *"It is essential that consideration is given to preserving confidentiality at the reporting stage. The possibility of unintentional (deductive) disclosure arises when cells with small numbers of patients are quoted. Applicants should note that, when reporting the data, CPRD policy is that no cell should contain <5 events."*

Baseline characteristics of exenatide once-weekly initiators

The basic demographics, co-morbidities and co-medications were described for exenatide once-weekly initiators identified in GOLD. Additional details on exenatide once-weekly initiation and exposure were also described.

All covariates used in this study are listed below.

Demographics and baseline characteristics:

(i) Gender
(ii) Age[ii]
(iii) Geographic area
(iv) Body Mass Index (BMI)[iii]
(v) Alcohol use[iv]
(vi) Smoking[v]
(vii) Practice based socioeconomic status data[vi]

Diabetes severity indicators assessed prior to initiation on once-weekly exenatide:

(i) Use of OAD (Other Anti-diabetic Drugs) medications, by type in the one year before

[ii] See Age in Annex 2.
[iii] See BMI in Annex 2.
[iv] See Alcohol in Annex 2.
[v] See Smoking in Annex 2.
[vi] See Socioeconomic status in Annex 2.

(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
(vi) HbA_{1C}[vii] measurements (most recent measurement in the six months before)
(vii) KDOQI stage of chronic kidney disease (assessed using the latest data recorded prior to initiation on exenatide)

Cardiovascular disease indicators assessed prior to initiation on once-weekly exenatide:

(i) Treated hypertension (i.e., Read code for hypertension ever before and prescribing of anti-hypertensives in the one year before)
(ii) Hyperlipidemia ever before
(iii) Ischemic heart disease (IHD) ever before
(iv) Myocardial infarction (MI) ever before
(v) Congestive heart failure ever before
(vi) Stroke ever before

Other indicators of co-morbidity and co-medication assessed prior to initiation on once-weekly exenatide:

(i) Number of laboratory tests performed in the one year before the index date
(ii) Evidence of pancreatic disease and thyroid disease ever before
(iii) History of gall bladder disease ever before
(iv) Symptom of liver enlargement or record of fatty liver ever before
(v) Number of lipid-lowering drugs in the one year before the index date

Follow-up and exposure:

(i) Mean duration of follow-up in years
(ii) Year in which exenatide once-weekly was initiated
(iii) Length of exposure in months to exenatide once-weekly

Follow-up was defined as the time in years from exenatide-weekly initiation until the earliest of the following: the date of diagnosis of one of the study outcomes, the end of the study or the end of data collection (i.e. last practice GOLD data collection, transfer out of practice date or date of death, whichever came first). The length of once-weekly exenatide exposure was calculated as the time in days from first once-weekly exenatide prescription in the study to the date of the last weekly exenatide prescription in the study, plus the median inter-prescription gap in days. The length of exposure in days was converted to months using a conversion of 30 days per month.

Incidence rates

Crude incidence rates (with 95% confidence intervals) of (a) any thyroid neoplasm, (b) benign thyroid neoplasm, (c) malignant thyroid neoplasm and (d) pancreatic cancer among exenatide once-weekly initiators were estimated overall and by age, gender and year of exenatide once-weekly initiation using a denominator of patient-years-at-risk.

[vii] See HbA1c in Annex 2.

Sub-Group Analysis

The main analysis was repeated among the sub-group of patients who were co-prescribed insulin analogues and exenatide once-weekly.

Any patient who received 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 was included in this sub-cohort. Additionally, any patient who received a prescription for an insulin analogue whilst 'exposed' to exenatide (see definition above) was also included in the sub-cohort.

Results

A total of **179** patients who initiated exenatide once-weekly between 1st July 2011 and 30th June 2014 were included in the main analysis. Baseline patient and demographic characteristics, and indicators of co-medications and co-morbidities at baseline for these individuals are described in Tables 1 and 2.

Analysis of the sub-cohort included **55** patients who were co-prescribed insulin analogues whilst being prescribed exenatide once-weekly. Characteristics, co-medications and co-morbidities for these individuals are described in Tables 5 and 6.

As would be expected in a population of patients with T2DM, the majority of patients in both the main (92.1%) and sub (98.2%) cohorts were aged 40 years or more. In addition, nearly all patients had BMIs indicative of obesity (91.1% in the main cohort and 92.7% in the sub cohort). Prior to initiation of exenatide-once weekly treatment, fewer than one in ten (8.4%) of patients in the main cohort had normal or optimally regulated blood glucose levels (i.e. HbA1c less than 7%). The proportion of patients in the sub-cohort with normal or optimally regulated blood glucose levels prior to exenatide once-weekly initiation was 5.5%.

The number of patients in the main cohort who initiated exenatide once-weekly between 1st July 2013 and 30th June 2014 was significantly smaller than in either of the preceding years (34 *vs* 96 for 2012-2013 and 49 for 2011-2012). However, over half (52.0%) of patients were prescribed exenatide once-weekly for 12 or more months during the study, which suggests that those who start exenatide once-weekly tend to continue taking exenatide once-weekly. A similar trend was observed in the sub-cohort of patients co-prescribed insulin analogues.

None of the patients had evidence of thyroid neoplasms (benign or malignant) or pancreatic cancer recorded on or after initiation of exenatide once-weekly. Incidence rates for these outcomes could not therefore be calculated; however, details on the numbers of patients and person-years-at-risk are provided in Table 4 for the main cohort and Table 8 for the sub-cohort. The total number of person-years-at-risk in the main and sub-cohorts were 246 person-years and 75 person-years, respectively.

References

1. Mann K, Raskin P. Exenatide extended-release: a once weekly treatment for patients with type 2 diabetes. *Diabetes Metab Syndr Obes* 2014; 7:229-39.

2. Alves C, Batel-Marques F, Macedo AF. A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer. *Diabetes Res and Clin Pract* 2012; 98(2): 271-284.

3. Dore D, Seeger J, Chan K. Incidence of health insurance claims for thyroid neoplasm and pancreatic malignancy in association with exenatide: signal refinement using active safety surveillance. *Ther Adv Drug Saf* 2012; 3(4):157-164.

Annex 1. Tables of Results

Main analysis

Table 1: Demographics and baseline characteristics of exenatide once-weekly initiators

Characteristic	Number (% of overall) [or otherwise specified]
Gender	
Male	95 (53.1%)
Female	84 (46.9%)
Age	
18-29	1 (0.6%)
30-39	13 (7.3%)
40-49	43 (24.0%)
50-59	48 (26.8%)
60-69	52 (29.1%)
70+	22 (12.3%)
Region	
North East	0 (0.0%)
North West	19 (10.6%)
Yorkshire & The Humber	3 (1.7%)
East Midlands	1 (0.6%)
West Midlands	8 (4.5%)
East of England	5 (2.8%)
South West	20 (11.2%)
South Central	21 (11.7%)
London	9 (5.0%)
South East Coast	29 (16.2%)
Northern Ireland	11 (6.1%)
Scotland	16 (8.9%)
Wales	37 (20.7%)
Body Mass Index (kg/m^2)	
Mean (SD)	39.1 (7.1)
Median (IQR)	38.4 (33.9 - 43.6)
Underweight (<20)	0 (0.0%)
Normal (20-<25)	1 (0.6%)
Overweight (25-<30)	15 (8.4%)
Obese (>=30)	163 (91.1%)
Unknown BMI	0 (0.0%)
Alcohol Use	
Non Drinker	20 (11.2%)

Ex Drinker	36 (20.1%)
Drinker	121 (67.6%)
Unknown Drinking Status	2 (1.1%)
Smoking Status	
Non Smoker	61 (34.1%)
Ex Smoker	86 (48.0%)
Smoker	32 (17.9%)
Unknown Smoking Status	0 (0.0%)
Socio-demographic Status (in quintiles)	
Q1 (Least Deprived)	25 (14.0%)
Q2	28 (15.6%)
Q3	37 (20.7%)
Q4	29 (16.2%)
Q5 (Most Deprived)	60 (33.5%)

Table 2: Indicators of co-morbidity and co-medication at baseline in exenatide once-weekly initiators

Indicator		Number (% of overall) [or otherwise indicated]
Diabetes Severity		
(i) OAD prescribed within one year prior to index date (by type)	Acarbose	3 (1.7%)
	Glinide	0 (0.0%)
	Metformin	163 (91.1%)
	Metformin & TZD	6 (3.4%)
	SU	86 (48.0%)
	TZD	43 (24.0%)
	Other OAD	0 (0.0%)
	Insulin (any)	57 (31.8%)
	Insulin (analogues only)	54 (30.2%)
(ii) Duration (months) of type 2 diabetes mellitus at index date	0 - 5	7 (3.9%)
	6 - 23	7 (3.9%)
	24 - 59	31 (17.3%)
	60+	134 (74.9%)
	Missing	0 (0.0%)
(iii) Peripheral neuropathy		14 (7.8%)
(iv) Nephropathy		62 (34.6%)
(v) Retinopathy		63 (35.2%)
(vi) HbA1c in the year prior to the index date	<5% (normal)	0 (0.0%)
	5% - <7% (well regulated)	15 (8.4%)
	7% - <8.5% (not optimally regulated)	40 (22.3%)
	8.5% - <10% (poorly regulated)	62 (34.6%)
	10% - <12% (very poorly regulated)	43 (24.0%)
	>=12%	15 (8.4%)
	Missing	0 (0.0%)
Chronic Kidney Disease (CKD)		
(i) Stage	1 (normal kidney function)	3 (1.7%)
	2 (mildly reduced kidney function)	6 (3.4%)
	3 (moderately reduced kidney function)	22 (12.3%)
	4 (severely reduced kidney function)	0 (0.0%)
	5 (very severe / end stage kidney failure)	0 (0.0%)
	Missing	148 (82.7%)
Cardiovascular disease		
(i) Treated hypertension (history and prescription of anti-hypertensives in the previous year)		26 (14.5%)
(ii) Hyperlipidaemia (ever before)		42 (23.5%)

(iii) Ischemic heart disease (ever before)		35 (19.6%)
(iv) Myocardial infarction (ever before)		15 (8.4%)
(v) Congestive heart failure (ever before)		5 (2.8%)
(vi) Stroke (ever before)		9 (5.0%)
Other indicators		
(i) Number of laboratory tests performed in the year before*	Mean (SD)	5.8 (3.9)
	Median (IQR)	5.0 (3.0-7.0)
(ii) Evidence of pancreatic or thyroid disease		26 (14.5%)
(iii) Gall bladder disease		22 (12.3%)
(iv) Symptom of liver enlargement or record of fatty liver		9 (5.0%)
(v) Number of lipid-lowering drugs prescribed in the year before**	Mean (SD)	8.7 (6.6)
	Median (IQR)	7.0 (5.0-11.0)

Notes:
** Laboratory tests on the same date were counted as one test.*
*** Lipid-lowering drug prescriptions issued on the same day were counted as a single prescription.*
OAD – Other Anti-diabetic Drug
SU – sulfonylureas
TZD – thiazolidinediones

Table 3: Follow-up and cumulative exenatide once-weekly exposure among exenatide once-weekly initiators, 1st July 2011 – 30th June 2014

	No. of patients (or otherwise specified)	Prop. of patients (or otherwise specified)
Total duration of follow-up (person-years)		
Mean (SD)	1.38	0.67
Year of exenatide once-weekly initiation		
1st July 2011 - 30th June 2012	49	27.4%
1st July 2012 - 30th June 2013	96	53.6%
1st July 2013 - 30th June 2014	34	19.0%
Cumulative exposure to exenatide once-weekly in months		
<3	38	21.2%
3-6	21	11.7%
7-11	27	15.1%
12-18	46	25.7%
>18	47	26.2%

Table 4a: Incidence rates of *any* thyroid neoplasm among exenatide once-weekly initiators, by gender, age group and year, 1st July 2011 – 30th June 2014
Table 4b: Incidence rates of *benign* thyroid neoplasm among exenatide once-weekly initiators, by gender, age group and year, 1st July 2011 – 30th June 2014
Table 4c: Incidence rates of *malignant* thyroid neoplasm among exenatide once-weekly initiators, by gender, age group and year, 1st July 2011 – 30th June 2014
Table 4d: Incidence rates of pancreatic cancer among exenatide once-weekly initiators, by gender, age group and year, 1st July 2011 – 30th June 2014

Demographic characteristic		No. subjects	Person years at risk	No. cases	Incidence rate	95% CI
Gender						
	Male	95	135.8	0	N/A	
	Female	84	110.4	0	N/A	
Age						
	18-29	1	1.95	0	N/A	
	30-39	13	13.1	0	N/A	
	40-49	43	61.3	0	N/A	
	50-59	48	63.3	0	N/A	
	60-69	52	74.4	0	N/A	
	70+	22	32.2	0	N/A	
Year						
	1st July 2011 - 30th June 2012	49	98.9	0	N/A	
	1st July 2012 - 30th June 2013	96	130	0	N/A	
	1st July 2013 - 30th June 2014	34	17.3	0	N/A	
All						
		179	246	0	N/A	

Sub-group analysis

Table 5: Demographics and baseline characteristics of exenatide once-weekly initiators who are co-prescribed insulin analogues

Characteristic	Number (% of overall) [or otherwise specified]
Total Patients	*55/179 (30.7%)*
Gender	
Male	31 (56.4%)
Female	24 (43.6%)
Age	
18-29	0 (0.0%)
30-39	1 (1.8%)
40-49	9 (16.4%)
50-59	17 (30.9%)
60-69	17 (30.9%)
70+	11 (20.0%)
Region	
North East	0 (0.0%)
North West	5 (9.1%)
Yorkshire & The Humber	1 (1.8%)
East Midlands	0 (0.0%)
West Midlands	3 (5.5%)
East of England	2 (3.6%)
South West	6 (10.9%)
South Central	5 (9.1%)
London	6 (10.9%)
South East Coast	7 (12.7%)
Northern Ireland	2 (3.6%)
Scotland	4 (7.3%)
Wales	14 (25.5%)
Body Mass Index (kg/m^2)	
Mean (SD)	37.2 (6.0)
Median (IQR)	36.1 (31.7 – 43.0)
Underweight (<20 kg/m^2)	0 (0.0%)
Normal (20 - <25 kg/m^2)	0 (0.0%)
Overweight (25 - <30 kg/m^2)	4 (7.3%)
Obese (≥30 kg/m^2)	51 (92.7%)
Unknown BMI	0 (0.0%)
Alcohol Use	
Non Drinker	6 (10.9%)

Ex Drinker	11 (20.0%)
Drinker	37 (67.3%)
Unknown Drinking Status	1 (1.8%)
Smoking Status	
Non Smoker	16 (29.1%)
Ex Smoker	30 (54.5%)
Smoker	9 (16.4%)
Unknown Smoking Status	0 (0.0%)
Socio-demographic Status (in quintiles)	
Q1 (Least Deprived)	4 (7.3%)
Q2	8 (14.5%)
Q3	15 (27.3%)
Q4	15 (27.3%)
Q5 (Most Deprived)	13 (23.6%)

Table 6: Indicators of co-morbidity and co-medication at baseline in exenatide once-weekly initiators who are co-prescribed insulin analogues

Indicator		Number (% of overall) [or otherwise indicated]
Diabetes Severity		
(i) OAD prescribed within one year prior to index date (by type)	Acarbose	1 (1.8%)
	Glinide	0 (0.0%)
	Metformin	50 (90.9%)
	Dual therapy (Metformin & TZD)	0 (0.0%)
	SU	7 (12.7%)
	TZD	5 (9.1%)
	Other OAD	0 (0.0%)
	Insulin (any)	53 (96.4%)
	Insulin (analogues only)	53 (96.4%)
(ii) Duration (months) of type 2 diabetes mellitus at index date	0 - 5	0 (0.0%)
	6 - 23	1 (1.8%)
	24 - 59	4 (7.3%)
	60+	50 (90.9%)
	Missing	0 (0.0%)
(iii) Peripheral neuropathy		10 (18.2%)
(iv) Nephropathy		21 (38.2%)
(v) Retinopathy		27 (49.1%)
(vi) HbA1c in the year prior to the index date	<5% (normal)	0 (0.0%)
	5% - <7% (well regulated)	3 (5.5%)
	7% - <8.5% (not optimally regulated)	8 (14.5%)
	8.5% - <10% (poorly regulated)	22 (40.0%)
	10% - <12% (very poorly regulated)	15 (27.3%)
	>=12%	4 (7.3%)
	Missing	0 (0.0%)
Chronic Kidney Disease (CKD)		
(i) Stage	1 (normal kidney function)	0 (0.0%)
	2 (mildly reduced kidney function)	3 (5.5%)
	3 (moderately reduced kidney function)	9 (16.4%)
	4 (severely reduced kidney function)	0 (0.0%)
	5 (very severe / end stage kidney failure)	0 (0.0%)
	Missing	43 (78.2%)
Cardiovascular disease		
(i) Treated hypertension (history and prescription of anti-hypertensives in the previous year)		8 (14.5%)

(ii) Hyperlipidaemia (ever before)		18 (32.7%)
(iii) Ischemic heart disease (ever before)		21 (38.2%)
(iv) Myocardial infarction (ever before)		11 (20.0%)
(v) Congestive heart failure (ever before)		3 (5.5%)
(vi) Stroke (ever before)		3 (5.5%)
Other indicators		
(i) Number of laboratory tests performed in the year before*	Mean (SD)	6.1 (4.1)
	Median (IQR)	5.0 (4.0-8.0)
(ii) Evidence of pancreatic or thyroid disease		8 (14.5%)
(iii) Gall bladder disease		7 (12.7%)
(iv) Symptom of liver enlargement or record of fatty liver		3 (5.5%)
(v) Number of lipid-lowering drugs prescribed in the year before**	Mean (SD)	11.0 (9.8)
	Median (IQR)	10.0 (6.0-13.0)

Notes:
** Laboratory tests on the same date were counted as one test.*
*** Lipid-lowering drug prescriptions issued on the same day were counted as a single prescription.*
OAD – Other Anti-diabetic Drug
SU – sulfonylureas
TZD – thiazolidinediones

Table 7: Follow-up and cumulative exenatide once-weekly exposure among exenatide once-weekly initiators who are co-prescribed insulin analogues, 1st July 2011 – 30th June 2014

	No. of patients (or otherwise specified)	Prop. of patients (or otherwise specified)
Total duration of follow-up (person-years)		
Mean (SD)	1.36	0.65
Year of exenatide once-weekly initiation		
1st July 2011 - 30th June 2012	14	25.5%
1st July 2012 - 30th June 2013	33	60.0%
1st July 2013 - 30th June 2014	8	14.5%
Cumulative exposure to exenatide once-weekly in months		
<3	14	25.5%
3-6	5	9.1%
7-11	7	12.7%
12-18	20	36.4%
>18	9	16.4%

Table 8a: Incidence rates of *any* thyroid neoplasm among exenatide once-weekly initiators who are co-prescribed insulin analogues, by gender, age group and year, 1st July 2011 – 30th June 2014
Table 8b: Incidence rates of *benign* thyroid neoplasm among exenatide once-weekly initiators who are co-prescribed insulin analogues, by gender, age group and year, 1st July 2011 – 30th June 2014
Table 8c: Incidence rates of *malignant* thyroid neoplasm among exenatide once-weekly initiators who are co-prescribed insulin analogues, by gender, age group and year, 1st July 2011 – 30th June 2014
Table 8d: Incidence rates of pancreatic cancer among exenatide once-weekly initiators who are co-prescribed insulin analogues, by gender, age group and year, 1st July 2011 – 30th June 2014

Demographic characteristic		No. subjects	Person years at risk	No. cases	Incidence rate	95% CI
Gender						
	Male	31	41.3	0	N/A	
	Female	24	33.7	0	N/A	
Age						
	18-29	0	0.00	0	N/A	
	30-39	1	1.11	0	N/A	
	40-49	9	11.6	0	N/A	
	50-59	17	23.2	0	N/A	
	60-69	17	25.1	0	N/A	
	70+	11	14.0	0	N/A	
Year						
	1st July 2011 - 30th June 2012	14	29.2	0	N/A	
	1st July 2012 - 30th June 2013	33	42.0	0	N/A	
	1st July 2013 - 30th June 2014	8	3.75	0	N/A	
All						
		55	75.0	0	N/A	

Annex 2. Glossary of Terms / Data Definitions

Acceptable Patients
Patients are labelled as 'acceptable' for use in research by a process that identifies and excludes patients with non-continuous follow up or patients with poor data recording that raises suspicion as to the validity of the patients record. Patient data is checked, for the following issues:

- An empty or invalid first registration date
- An empty or invalid current registration date
- Absence of a record for a year of birth
- A first registration date prior to their birth year
- A current registration date prior to their birth year
- A transferred out reason with no transferred out date
- A transferred out date with no transferred out reason
- A transferred out date prior to their first registration date
- A transferred out date prior to their current registration date
- A current registration date prior to their first registration date
- A gender other than Female/Male/Indeterminate
- An age of greater than 115 at end of follow up
- Recorded health care episodes in years prior to birth year
- All recorded health care episodes have empty or invalid event dates
- Registration status of temporary patients

If any of these conditions are true then the patient is labelled unacceptable, and is not recommended for use in research.

UTS date
The overall quality of data in practices is mediated by use of an 'up to standard' (UTS) date, which is deemed as the date at which data in the practice is considered to have continuous high quality data fit for use in research. This is mediated by an analysis on the total data in the practice, which is refreshed every time a new collection for a practice is processed into the database. It is based on two central concepts: assurance of continuity in data recording (gap analysis), and avoidance of use of data for which transferred out and dead patients have been removed (death recording).

Gap Analysis
To detect whether there are any meaningful gaps in the data it is necessary to look in more detail at single day gaps as well as longer gaps. A single day alone may reflect a situation where nothing was recorded that day at the practice, i.e. the practice was not open, such as on a bank holiday. A longer gap may reflect a situation where the practice did not offer a service and patients may have been treated elsewhere. If a meaningful gap is found, the earliest date after which there is no significant gap is identified.

Death Recording
It is expected that a standard number of deaths will be recorded at a practice over time. Assessment of gaps in death recording is performed taking the size of the practice into account. A safety margin is built in to account for both geographical and seasonal variation in death rates. If a meaningful gap is found, the earliest date after which there is no significant gap is identified.

The UTS date is set to the latest of these dates for each practice. The CPRD recommend that analyses are performed on data following the practice UTS date.

UTS follow up

UTS follow-up begins from the latest of the patient's registration date and the practice up-to-standard date. UTS follow-up ends at the earliest of the patient's death, transfer out of the practice, or practice last collection date.

HbA_{1c}

HbA_{1c} measurements are identified based upon either a recorded HbA_{1c} test or one of the following Read codes:

Read Code	Read Term
42W..11	Glycosylated Hb
42W..00	Hb. A1C - diabetic control
42W1.00	Hb. A1C < 7% - good control
42W3.00	Hb. A1C > 10% - bad control
42WZ.00	Hb. A1C - diabetic control NOS
42c..00	HbA1 - diabetic control
44TB.00	Haemoglobin A1c level
42W..12	Glycated haemoglobin
42W4.00	HbA1c level (DCCT aligned)
42c3.00	HbA1 level (DCCT aligned)
44TC.00	Haemoglobin A1 level
42W2.00	Hb. A1C 7-10% - borderline
66Ae.00	HbA1c target
66Ae000	HbA1c target level - IFCC standardised
44TL.00	Total glycosylated haemoglobin level
42c1.00	HbA1 7 - 10% - borderline control
42c0.00	HbA1 < 7% - good control
42c2.00	HbA1 > 10% - bad control
42W5.00	Haemoglobin A1c level - IFCC standardised

The following approach is used to deal with potentially invalid HbA1c measurements.

- Only tests recorded during UTS follow up are included
- All '0' values are treated as missing and all missing values are excluded
- Exact duplicates are excluded
- Units are converted to standard format using the formula (value/10.929)+2.15 for:
    - all values recorded using units relating to "mol" with a value>16
    - all values recorded using units relating to "mol" after 01/06/2009
    - all values with no unit recorded with a value>16 after 01/06/2009
- The conversion creates many duplicates since often patients have a second result recorded in % at the same time, therefore exact duplicates are again excluded
- Records with a value<3.4 are excluded
- Records with a value>16 are excluded

- Where there are duplicates on the same day, the highest value is used

HbA_{1c} values are then categorised as follows:

- <5% (“normal”)
- 5.0 - <7% (well regulated)
- 7.0 - <8.5% (not optimally regulated)
- 8.5 - <10% (poorly regulated)
- 10 - <12% (very poorly regulated)
- >= 12%
- missing

Age
Since only the year of birth is available in GOLD, age is calculated as the difference between the year of the index date and the birth year.

BMI
Body Mass Index is calculated from weight and height information. The closest height, weight and BMI measurements to the index date will be used. BMI is calculated using weight (kg) / (height (m)*height (m)), for patients aged at least 18 at the date of the height measurement. BMI measurements of <10 or >70 will be excluded.

Smoking status
Smoking status is calculated from records of smoking status, and from searching for smoking records in the patient’s history using a Read code list. Only records from before or on index date are included. Records are categorised into Non-Smoker, Ex-Smoker, and Smoker. An algorithm is used to determine the most appropriate category for patients. For example, when duplicate records on the same day differ, Smoker would be chosen over Ex-Smoker, which would be chosen over Non-Smoker.

Drinking Status
Alcohol consumption is calculated from records of drinking status, and from searching for alcohol consumption records in the patient’s history using a Read code list. Only records from before or on index date are included. Records are categorised into Non-Drinker, Ex-Drinker, and Drinker. An algorithm is used to determine the most appropriate category for patients. For example, when duplicate records on the same day differ, Drinker would be chosen over Ex-Drinker, which would be chosen over Non-Drinker.

Socioeconomic status (deprivation)
Deprivation is calculated using the postcode of the patient mapped at the small area level to the Index of Multiple Deprivation. The Index of Multiple Deprivation combines a number of indicators, chosen to cover a range of economic, social and housing issues, into a single deprivation score for each small area. The indicators are different for England, Scotland, Wales and Northern Ireland, but generally include income, employment, health, and the living environment. The quintiles relate to the country as a whole.

Annex 3. Code Lists for Study Outcomes

Thyroid Neoplasm

Read code	Read term	Any	Benign	Malignant
5A12.00	Thyroid tumour/metast irradiat	Yes	No	Yes
B53..00	Malignant neoplasm of thyroid gland	Yes	No	Yes
B7G..00	Benign neoplasm of thyroid gland	Yes	Yes	No
B7G..11	Adenoma of thyroid gland	Yes	Yes	No
B8yy000	Carcinoma in situ of thyroid gland	Yes	No	Yes
B924000	Neoplasm of uncertain behaviour of thyroid gland	Yes	Yes	No
BB5f.00	[M]Thyroid adenoma and adenocarcinoma	Yes	No	Yes
BB5f100	[M]Follicular adenocarcinoma NOS	Yes	No	Yes
BB5f111	[M]Follicular carcinoma	Yes	No	Yes
BB5f200	[M]Follicular adenocarcinoma, well differentiated type	Yes	No	Yes
BB5f300	[M]Follicular adenocarcinoma, trabecular type	Yes	No	Yes
BB5f600	[M]Papillary and follicular adenocarcinoma	Yes	No	Yes
BB5fz00	[M]Thyroid adenoma or adenocarcinoma NOS	Yes	Yes	No
ByuB.00	[X]Malignant neoplasm of thyroid and other endocrine glands	Yes	No	Yes
ZV10y15	[V]Personal history of malignant neoplasm of thyroid	Yes	No	Yes

Pancreatic Cancer

Read code	Read term
B162.00	Malignant neoplasm of ampulla of Vater
B17..00	Malignant neoplasm of pancreas
B170.00	Malignant neoplasm of head of pancreas
B171.00	Malignant neoplasm of body of pancreas
B172.00	Malignant neoplasm of tail of pancreas
B173.00	Malignant neoplasm of pancreatic duct
B174.00	Malignant neoplasm of Islets of Langerhans
B175.00	Malignant neoplasm, overlapping lesion of pancreas
B17y.00	Malignant neoplasm of other specified sites of pancreas
B17y000	Malignant neoplasm of ectopic pancreatic tissue
B17yz00	Malignant neoplasm of specified site of pancreas NOS
B17z.00	Malignant neoplasm of pancreas NOS
B717011	Endocrine tumour of pancreas
BB5B.00	[M]Pancreatic adenomas and carcinomas
BB5B011	[M]Nesidioblastoma
BB5B100	[M]Islet cell carcinoma
BB5B200	[M]Insulinoma NOS

BB5B300	[M]Insulinoma, malignant
BB5B400	[M]Glucagonoma NOS
BB5B500	[M]Glucagonoma, malignant
BB5B600	[M]Mixed islet cell and exocrine adenocarcinoma
BB5Bz00	[M]Pancreatic adenoma or carcinoma NOS
BB5C.00	[M]Gastrinoma and carcinomas
BB5C000	[M]Gastrinoma NOS
BB5C100	[M]Gastrinoma, malignant
BB5Cz00	[M]Gastrinoma or carcinoma NOS
BB5y300	[M]Apudoma