

# EXHIBIT 2



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## A meta-analysis of serious adverse events reported with exenatide and liraglutide: Acute pancreatitis and cancer

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### ABSTRACT

**Aims:** The association between GLP-1 agonists, acute pancreatitis (AP), any cancer and thyroid cancer is discussed. This meta-analysis was aimed at evaluating the risk of those serious adverse events associated with GLP-1 agonists in patients with type 2 diabetes.

**Methods:** Medline, EMBASE, Cochrane Library and clinicaltrials.gov were searched in order to identify longitudinal studies evaluating exenatide or liraglutide use and reporting data on AP or cancer. Odds ratios (ORs) were pooled using a random-effects model.  $I^2$  statistics assessed heterogeneity.

**Results:** Twenty-five studies were included. Neither exenatide (OR 0.84 [95% CI 0.58–1.22],  $I^2 = 30%$ ) nor liraglutide (OR 0.97 [95% CI 0.21–4.39],  $I^2 = 0%$ ) were associated with an increased risk of AP, independent of baseline comparator. The pooled OR for cancer associated with exenatide was 0.86 (95% CI 0.29, 2.60,  $I^2 = 0%$ ) and for liraglutide was 1.35 (95% CI 0.70, 2.59,  $I^2 = 0%$ ). Liraglutide was not associated with an increased risk for thyroid cancer (OR 1.54 [95% CI 0.40–6.02],  $I^2 = 0%$ ). For exenatide, no thyroid malignancies were reported.

**Conclusions:** Current available published evidence is insufficient to support an increased risk of AP or cancer associated with GLP-1 agonists. These rare and long-term adverse events deserve properly monitoring in future studies evaluating GLP-1 agonists.

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### 1. Introduction

Pharmacological treatment of type 2 diabetes mellitus usually requires the sequential addition of antihyperglycemic agents [1]. Both the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASDs) consensus algorithm for the treatment of type 2 diabetes mellitus recommends the initiation of metformin and a lifestyle modification program at the time of diagnosis [1]. Sulphonylureas, thiazolidinediones and insulin can be subsequently added to the therapy [1].

Glucagon-like peptide-1 (GLP-1) agonists are a new class of blood-glucose lowering drugs indicated for the treatment of type 2 diabetes mellitus [2,3]. The first in class, exenatide twice-daily (BID) (Byetta™, Amylin Pharmaceuticals, San Diego, CA, USA/Eli Lilly and Company, Indianapolis, IN, USA), was approved by the U.S. Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) in 2005 and 2006, respectively [4,5]. Lately, a once-weekly (QW) presentation of exenatide (Bydureon™) received a market authorization in Europe (2011) and in the United States (2012) [6,7]. Liraglutide (Victoza™, Novo Nordisk A/S, Bagsværd, Denmark) was authorized by EMA and FDA in 2009 and 2010,

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respectively [8,9]. During the clinical development programmes, the GLP-1 agonists have demonstrated the potential to address fasting and postprandial glucose control with weight loss and low risk of hypoglycaemia [5,7,9]. However, this new class of antihyperglycaemic drugs has demanded some attention since potentially, although rare, serious adverse events have been associated with their use [10].

Post-marketing spontaneous reports of acute pancreatitis among patients treated with exenatide BID have been submitted to FDA's Adverse Event Reporting System (FAERS) since 2005 [11]. Signal generation analyses of this database identified an increased risk for acute pancreatitis associated with exenatide [12,13]. However, further observational longitudinal studies did not confirm such findings [14–16]. The post-marketing case reports led to an update of the exenatide' product labeling, on request of FDA [17]. Acute pancreatitis was also reported in randomized controlled clinical trials (RCTs) with liraglutide [18].

Benign thyroid C-cell adenomas were observed in rodents treated with exenatide BID but no carcinomas were reported [5,10]. Thyroid tumors occurred in rats administered with exenatide QW in carcinogenicity studies [7]. During RCT, unspecified neoplasms have been reported in patients treated with exenatide BID [5]. For liraglutide, C-cell hyperplasia and thyroid cancer were observed in pre-clinical toxicology studies [9,19]. Several cases of thyroid cancer were also reported during the liraglutide clinical development programme [9,18]. When approved by FDA, liraglutide label carries a Black Box warning regarding the risk of thyroid c-cell cancer [8].

This study was aimed at evaluating the risk of acute pancreatitis, any cancer or thyroid cancer, associated with GLP-1 agonists, exenatide and liraglutide, by carrying out a meta-analysis based on both experimental and observational published studies.

## 2. Methods

### 2.1. Literature search

Medline and Cochrane Library were searched from its inception until May 24, 2012 in order to identify relevant studies which evaluated GLP-1 agonists holding a market authorization [4–9]. Text words, brand names and manufacturer's coded designations were used to identify the medicines. Only literature published in the English language was considered for inclusion in this analysis. In order to ensure that all studies were identified, a second electronic search in the Medline and EMBASE was performed. Search terms related with pancreatitis and with cancer were combined with the medicines designations priori stated. The search terms were identified by consulting the MedDRA dictionary [20]. Bibliographic references list of all relevant studies, meta-analyses and reviews were hand searched in order to identify additional eligible articles. The registration site [clinicaltrials.gov](http://clinicaltrials.gov) was searched in order to identify all studies with available results that evaluated exenatide or liraglutide in type 2 diabetes mellitus. We did not seek to identify safety information of GLP-1 agonists beyond published studies. All the studies reporting

zero events in the treatment and/or control group were included. The electronic databases search strategy is available in Supplemental, Table 1.

### 2.2. Study selection and quality assessment

Literature was searched and relevant studies were selected for further assessment. The studies inclusion criteria were: 1 – published in English language; 2 – RCT or longitudinal observational studies (case-control or cohort studies); 3 – patients of all ages with type 2 diabetes mellitus; 4 – comparison of GLP-1 agonists with a placebo or active control (oral hypoglycaemic agents or insulin) and 5 – effect estimates on acute pancreatitis or cancer associated with GLP-1 agonists use. Only studies with duration of at least 12 weeks were included.

The quality of the retrieved studies was assessed using the checklist proposed by Downs and Black [21]. Studies' methodological quality was assessed as high, moderate or low when the total score was  $\geq 20$ , from 10 to 19, and  $< 10$ , respectively. When more than one reference was found for the same study, methodological quality evaluation was based on the total set of information. Two investigators scored the studies independently. Disagreement was resolved by discussion and consensus with a third investigator.

### 2.3. Data extraction and outcomes assessed

Data on study design, study duration, characteristics of participants, antihyperglycaemic therapy (dosage and treatment duration) and estimated effect measures or specified outcomes was extracted.

The following outcomes were considered: acute pancreatitis, any cancer and thyroid cancer. For any cancer as an outcome, all the events defined as "Neoplasms benign, malignant and unspecified (including cysts and polyps)" according to the MedDRA dictionary were considered [20]. For thyroid cancer, all terms were considered as those defined in the MedDRA dictionary were taking into consideration [20].

### 2.4. Statistical analysis

A meta-analysis was performed by pooling odds ratios (ORs) with their 95% confidence intervals (CIs), using the DerSimonian and Laird random-effects model and assuming that OR was an unbiased estimate of the relative risk (RR) [22]. This model was chosen since the validity of tests of heterogeneity can be limited with a small number of component studies and it is more conservative than a fixed-effect model in the presence of between-studies heterogeneity. When more than one adjusted effect estimate was reported, the most adjusted estimate was used. For studies with more than one intervention-arm, the number of events and the number of exposures were added. The same was applied when studies with multiple controls were the case. Between-studies heterogeneity was assessed by calculating a chi-square test and the  $I^2$  measure of inconsistency [23]. When no events were reported in one or both groups, a continuity correction of 0.5 was added to each cell.

The publication bias was visually examined by a funnel plot and statistically evaluated by Egger's regression asymmetry test [24,25].

A sensitivity analysis was conducted to explore the influence of the following variables on the summary estimates: studies' design, studies' methodological quality scores, the nature of the comparators (placebo or active control) and different GLP-1 agonists dose regimens (weekly or daily). All reported P values are 2-sided with significance being set as less than 0.05.

Review Manager (RevMan) version 5.1.6 (Cochrane Collaboration, Oxford, UK) and Comprehensive Meta-analysis Version 2 (Biostat, Englewood, NJ, USA) were used for all statistical analysis.

### 3. Results

The flowchart of the search strategy criteria is presented in Fig. 1. The electronic databases searches returned 4373 possible eligible references. After excluding for duplicates and screening the titles and abstracts, 179 bibliographic references were selected and full reports were obtained and evaluated in detail against inclusion criteria. A final sample of 40 references was eligible for inclusion, corresponding to 25

studies. No further studies meeting the inclusion criteria were identified throughout the studies back references lists'. Of the included studies in the analysis, 3 were retrospective cohort and the remaining were RCT. Two studies directly compared exenatide and liraglutide [Supplement 13,14,21].

The main characteristics of the studies and their methodological quality are presented in Table 1. More than one article can be referred to one study. For some studies, the information from the public database [clinicaltrials.gov](http://clinicaltrials.gov) complemented that reported in published papers (e.g., length of follow-up). The methodological quality was considered "high" for 15 studies and "moderate" for the other 10 studies.

#### 3.1. Acute pancreatitis

Thirteen studies of exenatide reported acute pancreatitis outcomes (Fig. 2a). Pooling their estimates yielded an OR of 0.84 (95% CI 0.58–1.22). Similar results were found in the subgroup analysis according to study design for both RCT (OR 1.70, 95% CI 0.35–8.29) and retrospective cohorts (OR 0.79, 95% CI 0.49–1.27) (Table 2). Between-studies heterogeneity accounted for 30% ( $P = 0.20$ ) of variation in treatment effect, mainly among observation studies ( $I^2 = 70\%$ ,  $P = 0.03$ ) than between RCT ( $I^2 = 0\%$ ,  $P = 0.76$ ). The results did not significantly change from the initial estimates when stratification

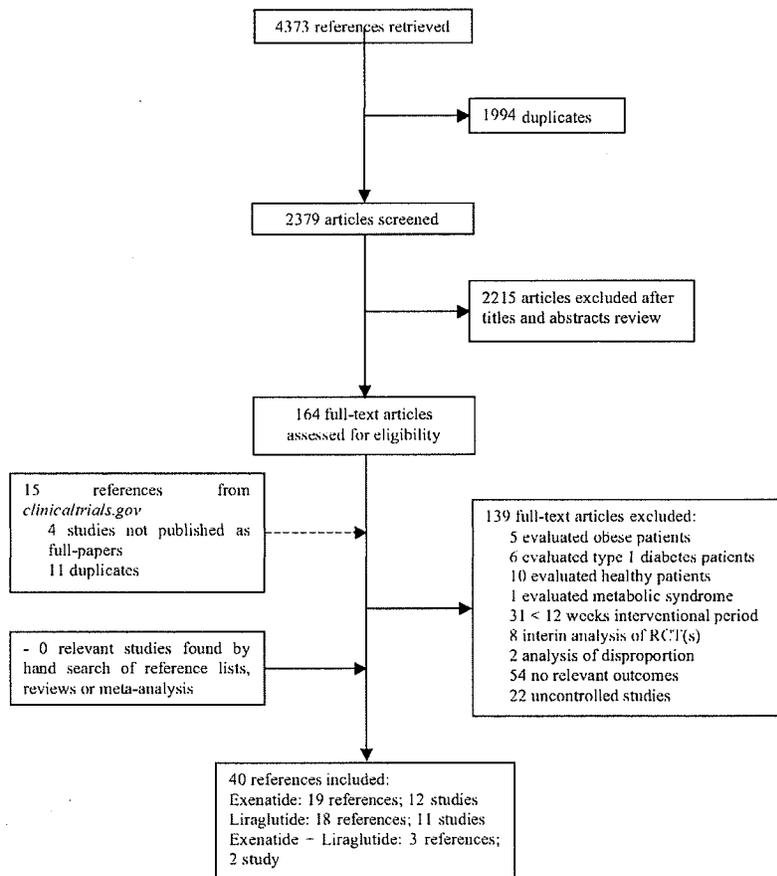


Fig. 1 – Flow diagram of identification of studies for inclusion.

**Table 1 - Characteristics of the studies included in the meta-analysis.**

Study <sup>a</sup>	Study design <sup>b</sup>	Population	Drugs tested		Duration (weeks)	Age mean (years)	Female %	Patients <sup>c</sup> (n, ID/C)	Cancer (n, ID/C)	Acute pancreatitis (n, ID/C)	M.Q.
			Intervention	Control							
Liraglutide 1860-LIRA-DPP-4 <sup>1,2,3</sup> (NCT00700817)	RCT, open-label, multicenter	Adults, aged 18-80 years, uncontrolled with METF	Liraglutide (1.2, 1.8 mg)	Sitagliptin	52	Lira 1.2:55.9 Lira 1.8:47.5 Sita: 45.2	Lira 1.2:48.4	439/219	5/1	1/0	22
LEAD-3 MONO <sup>4,5,6</sup> (NCT00294723)	RCT, open-label, multicenter	Adults, aged 18-80 years	Liraglutide (1.2, 1.8 mg)	Glimepiride	104	Lira 1.2:53.7 Lira 1.8:51.0 Glime: 46.0	Lira 1.2:53.0	497/248	12/2	3/0	22
Yang et al., 2011 (NCT00614120) <sup>7,8</sup>	RCT, double-blind, multicenter	Adults, aged 18-80 years, uncontrolled with METF	Liraglutide (0.6, 1.2, 1.8 mg)	Glimepiride	16	Lira 0.6:53.5 Lira 1.2:53.7 Lira 1.8:51.0 Glime: 46.0	Lira 0.6:45.9	697/231	2/1	0/0	19
Seino et al., 2010 <sup>9,10</sup> (NCT00393718)	RCT, double-blind, multicenter	Japanese adults, ≥20 years of age	Liraglutide (0.9 mg)	Glibenclamide	24	Lira 1.2:53.5 Lira 1.8:52.7 Glime: 53.6	Lira 1.2:45.1 Lira 1.8:46.2 Glime: 41.6	268/132	6/3	0/0	17
LEAD-5 met + SU <sup>11</sup>	RCT, double-blind, multicenter	Adults, aged 18-80 years, had T2 DM, uncontrolled with METF and GLI-MEP	Liraglutide (1.8 mg)	Insulin glargine/placebo	26	Lira: 58.2 Gliben: 58.5 Lira: 57.6	Lira: 32.0 Gliben: 35.0 Lira: 43.0	230/346	NR	0/0	23
LEAD-4 met + TZD <sup>12</sup>	RCT, double-blind, multicenter	Adults, aged 18-80 years, had T2 DM, uncontrolled with METF and ROSI	Liraglutide (1.2, 1.8 mg)	Placebo	26	Placebo: 57.5 Insulin: 57.5 Lira 1.2:55.0	Placebo: 51.0 Insulin: 40.0 Lira 1.2:43.0	356/177	NR	0/0	21

LEAD-6 <sup>13,14</sup> (NCT00518882)	RCT, open-label, multicenter	Adults, aged 18-80 years, uncontrolled with METF or SU or both	Liraglutide (1.8 mg)	Exenatide BID (10 µg)	26	Lira: 56.3 Lira: 51.0 235/232	3/0	0/0	23
LEAD-1 SU <sup>15</sup>	RCT, double-blind, multicenter	Adults, aged 18-80 years, had T2 DM, uncontrolled with GLI-MEP	Liraglutide (0.6, 1.2, 1.8 mg)	Placebo/ rosiglitazone	26	Exe: 57.1 Lira 0.6:55.7 695/345 Lira 1.2:57.7 Lira 1.8:55.6 Placebo: 54.7 Rosi: 56.0 Lira 0.6: 56.0 Lira 1.2:55.0 Lira 1.8:47.0 Placebo: 53.0 Rosi: 53.0 Lira 0.6: 38.0 Lira 1.2: 46.0 Lira 1.8: 41.0 Glime: 57.0 Placebo: 43.0 Placebo: 56.0 Lira 0.1: 31.1 180/46	NR	0/0	20
LEAD-2 <sup>16,17</sup> (NCT00318461)	RCT, double-blind, multicenter	Adults, aged 18-80 years, uncontrolled with METF	Liraglutide (0.6, 1.2, 1.8 mg)	Glimepiride/ placebo	26	Lira 0.1: 56.5 Lira 0.3: 56.8 Lira 0.6: 60.0 Lira 0.9: 55.5 Placebo: 57.5 Lira 0.6: 59.1 Lira 0.6: 39.8 176/88	9/2	1/1	21
Seino et al., 2008 <sup>18</sup>	RCT, double-blind, multicenter	Japanese adults, aged 20-75 years, had T2 DM	Liraglutide (0.1, 0.3, 0.6, 0.9 mg)	Placebo	14	Lira 0.9: 61.3 Placebo: 58.6 Lira 1.8: 57.7 Glime: 57.7 Placebo: 35.3 Placebo: 60.3 Lira: 56.7 450/461	1/0	NR	22
NCT00395746 <sup>19</sup>	RCT, double-blind, multicenter	Japanese adults, ≥20 years of age, uncontrolled with SU	Liraglutide (0.6, 0.9 mg)	Placebo	52	Lira 0.9: 61.3 Placebo: 58.6 Lira 1.8: 57.7 Glime: 57.7 Placebo: 35.3 Placebo: 60.3 Lira: 56.7 450/461	1/2	0/0	16
NCT00620282 <sup>20</sup>	RCT, double-blind, multicenter	Adults, aged 40-70 years, uncontrolled with METF	Liraglutide (1.8 mg)	Glimepiride/ placebo	12	Lira 0.9: 61.3 Placebo: 58.6 Lira 1.8: 57.7 Glime: 57.7 Placebo: 35.3 Placebo: 60.3 Lira: 56.7 450/461	0/1	0/0	17
NCT01029886 <sup>21</sup>	RCT, open-label, multicenter	Adults, ≥18 years of age, uncontrolled with METF, SU or both or METF and PIO	Liraglutide (1.8 mg)	Exenatide QW	26	Lira: 56.7 Lira: 45.5 450/461	0/2	0/1	17

Table 1 (Continued)

Study <sup>a</sup>	Study design <sup>b</sup>	Population	Drugs tested		Duration (weeks)	Age mean (years)	Female %	Patients <sup>c</sup> (n, ID/C)	Cancer (n, ID/C)	Acute pancreatitis (n, ID/C)	M.Q.
			Intervention	Control							
Exenatide Wentzen et al., 2012 <sup>22</sup>	Retrospective cohort study	Patients with ≥9 months of enrollment without claims for prior pancreatitis and a claim for a new antidiabetic between 03/2005 and 03/2009	Exenatide BID	Other ADs (2 mg)	212	Exe: 56.6 Exe: 52.0	Exe: 44.9 Exe: 58.0	24,237/457797	NR	46/802	16
Dore et al., 2011 <sup>23,24</sup> (NCT01077323)	Retrospective cohort study	Patients without claims for prior pancreatic disease and complete medical and pharmacy benefits between 09/2004 and 12/2007	Exenatide BID	Other ADs	123	Others ADs: 51.0 Exe: UTD	Others ADs: 53.0 Exe: 55.9	25,719/234536	NR	11/223	16
Buse et al., 2011 <sup>25,26</sup> (NCT00765817)	RCT, double-blind, multicenter	Adults, ≥18 years of age, had T2 DM, uncontrolled with IG with or without METF and/or PIO	Exenatide BID	Placebo	30	Others ADs: UTD Exe: 59.0	Others ADs: 49.0 Exe: 49.0	137/122	0/0	0/0	24
Gill et al., 2010 <sup>27,28</sup> (NCT00516074)	RCT, double-blind, multicenter	Adults, aged 18-75 years, had T2 DM, uncontrolled with METF or a THIAZ or both	Exenatide BID (5-10 µg)	Placebo	12	Placebo: 59.0 Exe: 57.0	Placebo: 36.0 Exe: 32.0	28/26	0/0	0/0	20

Author	Study Design	Population	Intervention	Comparator	Primary Outcome	Secondary Outcome	Other ADs	Exenatide BID	Others ADs	76	Exe: 51.4	Exe: 56.5	6545/16244	NR	22/65	15
Garg et al., 2010 <sup>29</sup>	Retrospective cohort study	Patients aged 18-63 years, with pharmacy and medical claims data for a continuous between 01/2007 and 06/2009	Exenatide BID	Others ADs												
Gallwitz et al., 2011 <sup>30,31</sup> (NCT00494954)	RCT, open-label, multicenter	Adults, aged 18-90 years, uncontrolled with METF	Exenatide BID (5-10 µg)	Premixed insulin aspartat					Others ADs: 52.9 Exe: 57.0	26	Others ADs: 42.8 Exe: UTD	247/233	2/0	NR		13
DURATION-3 <sup>32,33</sup>	RCT, open-label, multicenter	Adults, ≥18 years of age, uncontrolled with METF or METF and SU	Exenatide QW (2 mg)	Insuline glargine					PIA: 57.0 Exe: 58.0	84	PIA: UTD Exe: 48.0	233/223	1/0	1/0		23
DURATION-2 <sup>34</sup>	RCT, double-blind, multicenter	Adults, ≥18 years of age, uncontrolled with METF	Exenatide QW (2 mg)	Sitagliptin/pioglitazone					IG: 58.0 Exe: 52.0	26	IG: 45.0 Exe: 44.0	160/331	0/1	0/2		25
LEAD-6 <sup>13,14</sup> (NCT00518882)	RCT, open-label, multicenter	Adults, aged 18-80 years, uncontrolled with METF or SU or both	Exenatide BID (10 µg)	Liraglutide (1.8 mg)					Sitra: 52.0 Pio: 53.0 Exe: 57.1	26	Sitra: 48.0 Pio: 52.0 Exe: 45.0	232/235	0/3	0/0		23
Kadowaki et al., 2009 <sup>35</sup>	RCT, double-blind, multicenter	Japanese adults, aged 20-75 years, had T2 DM, uncontrolled with SU alone or in addition to a BIG or a THIAZ	Exenatide BID (2.5, 5, 10 µg)	Placebo					Lira: 56.3 Exe 2.5: 62.2	12	Lira: 51.0 Exe 2.5: 29.7	111/40	NR	0/0		21
Bunck et al., 2009 <sup>36,37</sup> (NCT00097500)	RCT, open-label, multicenter	Adults, aged 30-75 years, uncontrolled with METF	Exenatide BID (5-10 µg)	Insuline glargine					Exe 5: 60.7 Exe 10: 57.8 Placebo: 60.5 Exe: 58.4	52	Exe 5: 32.4 Exe 10: 37.8 Placebo: 25.0 Exe: 36.1	36/33	0/0	1/0		21
									IG: 58.3		IG: 33.3					

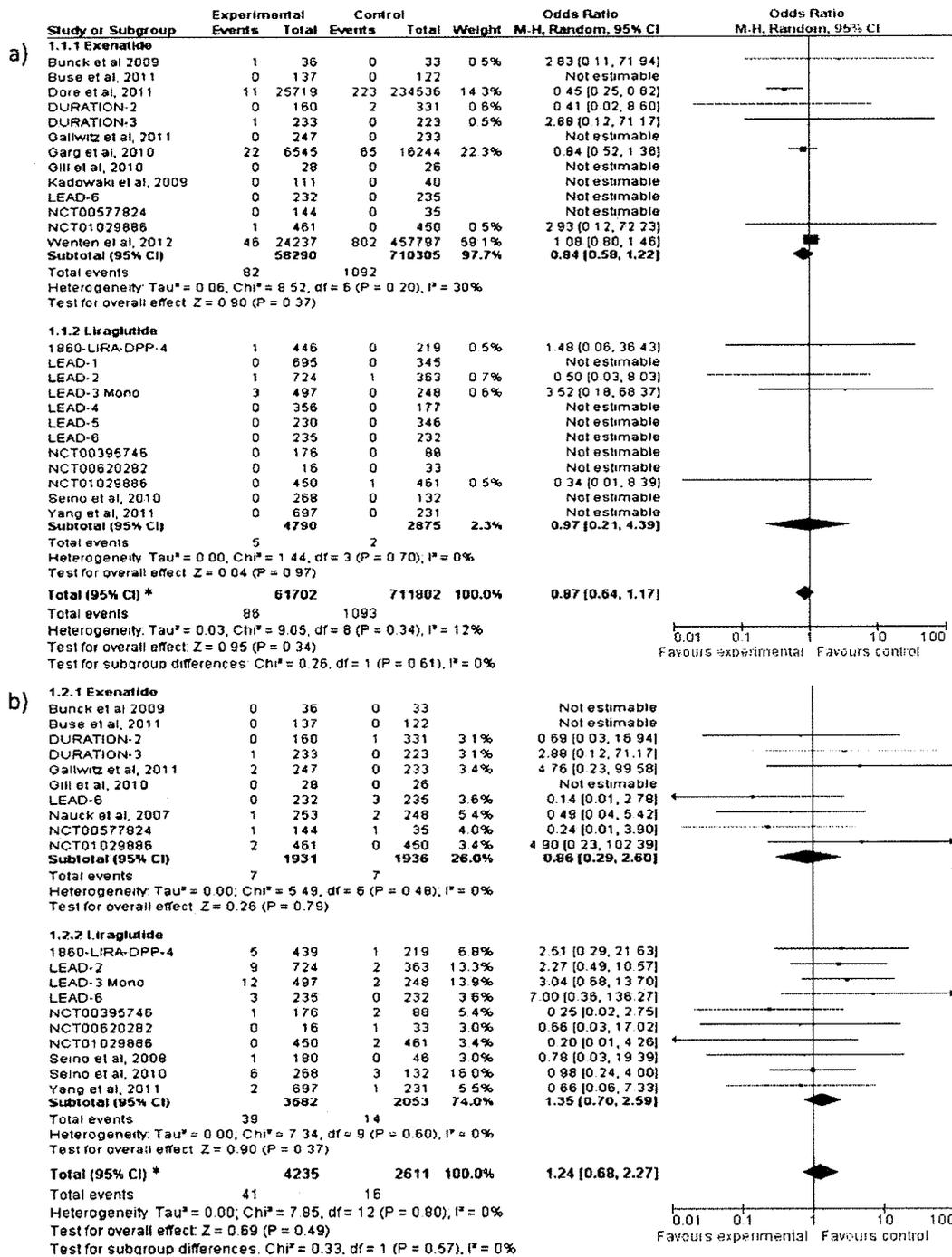
**Table 1 (Continued)**

Study <sup>a</sup>	Study design <sup>b</sup>	Population	Drugs tested		Duration (weeks)	Age mean (years)	Female %	Patients <sup>c</sup> (n, ID/C)	Cancer (n, ID/C)	Acute pancreatitis (n, ID/C)	M.Q.
			Intervention	Control							
Nauck et al., 2007 <sup>38</sup>	RCT, open-label, multicenter	Adults, aged 30-75 years, uncontrolled with METF and a SU	Exenatide BID (5-10 µg)	Biphasic insulin aspartat	52	Exe: 59.0	Exe: 47.0	253/248	1/2	NR	20
NCT00577824 <sup>39,40</sup>	RCT, double-blind, multicenter	Japanese adults, aged 20-75 years, uncontrolled with SU alone or in addition with a BIG or a THIAZ	Exenatide BID (5, 10 µg)	Placebo	24	BIAsp: 58.0 Exe 5: 58.5	BIAsp: 51.0 Exe 5: 31.9	144/35	1/1	0/0	17
NCT01029886 <sup>21</sup>	RCT, open-label, multicenter	Adults, ≥18 years of age, uncontrolled with METF, SU or both or METF and PIO	Exenatide QW (2 mg)	Liraglutide (1.8 mg)	26	Exe 10: 59.4 Placebo: 56.3 Exe: 56.6	Exe 10: 31.9 Placebo: 31.4 Exe: 44.9	461/450	2/0	1/0	17
						Lira: 56.7	Lira: 45.5				

<sup>a</sup> References for the studies displayed in this table are listed in Supplement 2.

<sup>b</sup> Concealment assignment is referring to the most recent studies' publication. Studies could be initially double-blinded and then become open-label in the extension phase.

<sup>c</sup> Number of patients included in the safety analysis; ID - intervention drug; C - control; n for "Acute Pancreatitis" and "Cancer", represents the number of patients; M.Q. - methodological quality assessment; NR - not reported; the studies LEAD-6 and NCT01029886 compared liraglutide with exenatide. Data from this study was not included in the GLP-1 receptor agonists drug class outcomes estimates; s.c. - subcutaneously; p.o. - orally; Lira - liraglutide; Sita - sitagliptin; T2 DM - type 2 diabetes mellitus; Glime - glimepiride; SU - sulphonylurea; Gliben - glibenclamide; ROSI - rosiglitazone; Exe - exenatide; METF - metformin; GLIMEP - glimepiride; PIA - premixed insulin aspartat; UTD - unable to determine; IG - insulin glargine; Sita - sitagliptin; PIO - pioglitazone; BIAsp - biphasic insulin aspartat; BIG - biguanide; THIAZ; thiazolidinedione; Ins - insulin; Ads - antidiabetic drugs.



\* For GLP-1 receptor agonists overall pooled results. LEAD-6 and NCT01029886 studies were not included

Fig. 2 – Pooled odds ratios (ORs) and 95% CIs of (a) acute pancreatitis and (b) overall cancer associated with GLP-1 agonists.

according to different controls, exenatide dose regimens or when only high methodological quality studies were considered. Non-significant between-studies heterogeneity was observed (Table 2).

Twelve liraglutide RCT reported acute pancreatitis as an outcome (Fig. 2a). The estimated OR for liraglutide and acute pancreatitis was 0.97 (95% CI 0.21–4.39). No significant between-studies heterogeneity was observed. The sensitivity

**Table 2 – Pooled odds ratios (ORs) and 95% CIs of acute pancreatitis and cancer associated with GLP-1 agonists.**

GLP-1 receptor agonists	Studies	Odds ratio (OR)		Heterogeneity		Publication bias <sup>a</sup>	
		N	95% CI	P	P	I <sup>2</sup>	P
<b>Acute pancreatitis</b>							
<b>Exenatide</b>							
All studies	13		0.84 [0.58, 1.22]	0.37	0.20	30%	0.94
RCTs	10		1.70 [0.35, 8.29]	0.51	0.76	0%	0.01
Retrospective cohorts	3		0.79 [0.49, 1.27]	0.32	0.03	70%	0.22
vs. Insulin	3		2.86 [0.29, 27.86]	0.37	0.99	0%	–
vs. OADs	2		0.82 [0.51, 1.33]	0.43	0.65	9%	–
Twice-daily	10		0.81 [0.51, 1.27]	0.36	0.06	59%	0.64
Once weekly	3		1.45 [0.24, 8.90]	0.69	0.60	0%	0.01
High quality	7		1.42 [0.23, 8.81]	0.70	0.61	0%	0.09
<b>Liraglutide</b>							
All studies	12		0.97 [0.21, 4.39]	0.97	0.70	0%	0.97
vs. Placebo	6		0.51 [0.02, 12.54]	0.68	–	–	–
vs. OADs	3		1.12 [0.20, 6.23]	0.89	0.50	0%	0.58
High quality	3		1.31 [0.24, 7.24]	0.76	0.63	0%	0.63
GLP-1 agonists	21		0.87 [0.64, 1.17]	0.34	0.34	12%	0.93
<b>Cancer</b>							
<b>Exenatide</b>							
All studies	10		0.86 [0.29, 2.60]	0.79	0.48	0%	0.33
vs. Placebo	3		0.24 [0.01, 3.90]	0.31	–	–	–
vs. OADs	1		0.69 [0.03, 16.94]	0.82	–	–	–
vs. Insulin	4		1.48 [0.29, 7.52]	0.64	0.46	0%	0.22
Twice-daily	7		0.50 [0.12, 2.05]	0.34	0.38	3%	0.78
Once weekly	3		2.20 [0.36, 13.53]	0.40	0.67	0%	0.49
High quality	7		0.56 [0.13, 2.37]	0.43	0.60	0%	0.67
<b>Liraglutide</b>							
All studies	10		1.35 [0.70, 2.59]	0.37	0.60	0%	0.27
vs. Placebo	4		0.53 [0.17, 1.65]	0.28	0.86	0%	0.72
vs. OADs	6		1.56 [0.74, 3.32]	0.24	0.76	0%	0.82
High quality	5		2.60 [1.08, 6.27]	0.03	0.90	0%	0.84
GLP-1 agonists	16		1.24 [0.68, 2.27]	0.49	0.80	0%	0.23

<sup>a</sup> Egger's regression asymmetry test. For GLP-1 agonists pooled results, both LEAD-6 and NCT01029886 studies were not included.

analysis according to different controls and the methodological quality of the studies did not significantly change the results (Table 2).

No significant risk reduction was observed in acute pancreatitis for both GLP-1 agonists (OR 0.87, 95% CI 0.64–1.17).

### 3.2. Any cancer

Ten RCT studying exenatide reported cancer outcomes (Fig. 2b). Exenatide was not associated with a significant risk of cancer development (OR 0.86, 95% CI 0.29–2.60). The sensitivity analysis according to the different controls, therapeutic regimen and the methodological quality of the studies did not significantly change the results (Table 2).

Ten RCT with liraglutide in type 2 diabetes mellitus reported cancer outcomes (Fig. 2b). Liraglutide was associated with a statistically non-significant 35% increased risk for any cancer development (OR 1.35, 95% CI 0.70–2.59). When liraglutide was compared with different controls, the results did not become statistically significant. However, the stratification of the results becomes statistically significant when only methodological studies of high quality were considered (OR 2.60, 95% CI 1.08–6.27) (Table 2).

No significant risk reduction was observed in cancer for both GLP-1 agonists (OR 1.24, 95% CI 0.68–2.27) and no

significant heterogeneity was observed in any of the comparisons (Table 2).

### 3.3. Thyroid cancer

None of the studies evaluating exenatide reported cases of thyroid cancer. Of the studies evaluating liraglutide, five reported cases of thyroid cancer. Nine patients treated with liraglutide were diagnosed with thyroid cancer comparing to one patient who developed this type of cancer and was treated with glimepiride [Supplement 4–6, 9, 10, 13, 14, 16–18]. The OR for thyroid cancer occurrence associated with liraglutide treatment was 1.54 (95% CI 0.40–6.02,  $P = 0.53$ ,  $I^2 = 0\%$ ).

### 3.4. Publication bias assessment

Egger's asymmetry test was not statistically significant for the primary or and most subgroup analyses but was significant for the analysis among exenatide RCT ( $P = 0.01$ ) and for once-weekly exenatide regimen studies ( $P = 0.01$ ) (Table 2). Subjective evaluation of publication bias was based on the visual inspection of funnel plot. Few studies were considered for both the analyses, not allowing firm conclusions about the potential publication bias. Regarding cancer risk assessment, large studies are possibly absent for both exenatide and liraglutide.

#### 4. Discussions

The results of this meta-analysis suggest that neither exenatide nor liraglutide increase the risk for acute pancreatitis, when used in the treatment of type 2 diabetes mellitus. However, no conclusions can be drawn since the analysis is based on small studies, possibly underpowered to detect rare adverse events.

Our findings are in line with those reported in longitudinal observational studies which evaluated the risk for acute pancreatitis associated with exenatide [14–16]. The rates of acute pancreatitis in those studies were less than 0.5%, indicating that this is a rare adverse event. Our search did not find post-market observational studies for liraglutide.

Although evidence of association has not been established between GLP-1 agonists and acute pancreatitis, a few potentially confounding factors should be considered. Nausea, abdominal discomfort and vomiting are adverse drug reactions known to be associated with GLP-1 agonists use [5,7,9]. Since these events are also symptoms of acute pancreatitis, its recognition and appropriately diagnose may become difficult [26]. We only included studies with patients diagnosed with type 2 diabetes mellitus. It was recently documented that having type 2 diabetes puts patients in a higher risk of developing acute pancreatitis, independently of the drug therapy [27]. This may raise the question of whether the cases of acute pancreatitis are due to GLP-1 agonists therapy, to type 2 diabetes or to risk factors commonly seen in patients with type 2 diabetes – hypertriglyceridaemia, hyperlipidaemia, obesity, or concomitant medicines [28]. Considering that GLP-1 agonists were initially approved as type 2 diabetes add-on therapy and the recommendations of clinical guidelines, patients receiving GLP-1 agonists are more likely to be at more advanced stages of the disease, which increases the risk for pancreatitis, the potential for confounding by indication may be increased, particularly when observational studies are the case [1,15]. Based on spontaneous reports of adverse drug reactions, FDA recommended that the prescribing information of exenatide should include a warning about the risk of acute pancreatitis [17]. Liraglutide' prescribing information also includes a warning about the risk of pancreatitis, without a specific mention to its onset, type or severity [29]. This meta-analysis did not find any increased risk for acute pancreatitis associated with both GLP-1 agonists. Labeling change of exenatide regarding acute pancreatitis required by FDA was supported by spontaneous reports. Therefore, if the increased risk exists, the meta-analysis is unable to identify such risk, since spontaneous reporting data is not considered in the meta-analysis methodology. Similarly the FDA required the market authorization holder of liraglutide to conduct post-approval mechanistic animal studies along with a pharmacoepidemiologic study in order to better assess the risk of acute pancreatitis [18].

Several studies were conducted aiming to explain the mechanisms by which acute pancreatitis could be developed. Butler et al. presented a theoretical model on which GLP-1 agonists could amplify the pancreatic ductal replication already increased by type 2 diabetes mellitus or obesity [30,31]. This would increase the risk for low grade chronic

pancreatitis that predisposes to acute pancreatitis or pancreatic carcinoma. However, the results of preclinical studies were contradictory, remaining unknown if GLP-1 agonists are associated with a specific pharmacological mechanism that may cause pancreatitis [32–34]. In order to avoid misclassification bias, and since the results of pre-clinical studies have shown to be contradictory, only cases reported as acute pancreatitis were included in this meta-analysis.

The possible carcinogenic effect of GLP-1 agonists observed during the pre-clinical studies should be properly evaluated. Moreover, the analysis of disproportion of the FDA-AERS database performed by Elashoff et al. demonstrated an increased risk for thyroid cancer associated with exenatide [12]. This meta-analysis did not identify an increased risk for any cancer associated with exenatide. The risk remained unchanged when the analysis was stratified according to the therapeutic regimens or different comparators. Regarding liraglutide exposure, no difference was observed when data from all studies was integrated or when the results were stratified according to the type of comparator. However, sensitivity analysis restricted to five high methodological quality studies showed an increased risk of cancer from all causes in patients treated with liraglutide. Caution should be taken when interpreting this result, since is the only significant association found, suggesting a possible chance of finding. Several instruments have been developed in order to assess the methodological quality of the studies [35]. The scale of Downs and Black was chosen since it is able to assess both experimental and observational studies [21].

Although the total number of cancer events was found to be low, a divergence between the risk of cancer associated with exenatide and liraglutide was identified (–14% for exenatide and 35% for liraglutide, both non-significant) (Table 2). Such findings deserve further careful attention. Moreover, when only high quality studies were considered, this difference increases. The present evaluation is based only in data from RCT since observational studies were not identified in our search strategy. Clinical trials are able to identify the most frequent and common adverse events that occurred during the intervention administration. However, considering cancer as a long-latency event, the duration of RCT and the short period between initial liraglutide exposure and malignancies diagnosis do not allow the establishment of a reliable causality between liraglutide exposure and cancer. No cases of C-cell lesions in thyroid have been documented in patients treated with exenatide. An increased proportion of thyroid carcinomas in patients treated with liraglutide have been reported in the included studies when compared with controls. However, the increased risk was non-statistically significant. As Drucker et al. previously stated, the small number of cases and the lack of biological plausibility raise some doubts between the use of GLP-1 agonists, namely liraglutide, and thyroid cancer occurrence [10]. Moreover, the effects of this drug in humans, particularly in the human thyroid gland, are unknown and difficult to be extrapolated from pre-clinical studies, despite the C-cell hyperplasia in rats [36]. The findings of this meta-analysis enhance the need for long-term well-designed epidemiological studies devoted to assess the risk for cancer

associated with GLP-1 agonists, including thyroid cancer during liraglutide exposure. Additional studies in animals and the establishment of a cancer registry database to monitor the incidence of medullary thyroid cancer associated with liraglutide was required by the FDA [18].

This meta-analysis may be subject to several limitations. Of the 22 RCT included, only one included the clinical evaluation of pancreatitis. Despite two RCT have evaluated the calcitonin levels, none of them were designed to prospectively monitor for malignancies. Pancreatitis and cancer were not defined as an initially outcome measure of RCT. These events were recorded as serious adverse events. The absence of malignancies and/or pancreatitis pre-defined diagnostic criteria can lead to missing events. Moreover, patients enrolled in the RCT are usually younger and with less comorbidities, being at a lower risk for developing the adverse events studied in this meta-analysis when compared with the average patients with type 2 diabetes observed on routine clinical practice. Residual confounding in the included observational studies may extend to the results of this meta-analysis.

Different controls were identified in the RCT included in this meta-analysis and they might be associated with different risks for acute pancreatitis or cancer, such the case of gliptins or pioglitazone. Because of the heterogeneity of comparators and the relatively small number of acute pancreatitis and cancer events reported in the studies, the stratification of the results at this level is difficult.

Publication bias with regard to acute pancreatitis and cancer is difficult to assess with few studies. In two acute pancreatitis analyses, the results were significant. This may be the case of RCT unpowered to detect rare events and subsequently creating difficulties in adverse events assessments. The European Public Assessment Report (EPAR) of exenatide BID reports that several neoplasms occurred in patients treated with exenatide BID during the clinical development programme, without specifying its type [5]. We were unable to find such data in published studies [37–39]. This suggests that publication bias may be present in our meta-analysis despite non-significant results observed for this outcome in the Egger's regression asymmetry test. We did not seek to collect data beyond that which is published. However, non-publication of events of such severity turns difficult the correct benefit/risk rate assessment, and in particular the assessment of the risk for cancer and its subtypes.

Current available published evidence is insufficient to support an increased risk of acute pancreatitis or an increased risk of cancer from all causes associated with GLP-1 agonists. However, there is a growing body of evidence from postmarketing spontaneous reports. Physicians and patients should remain vigilant for episodes of acute pancreatitis or cancer and report any events to the correspondent pharmacovigilance system. Since trials' size, duration and design may not be appropriate to accurately assess the risk of rare or long-term adverse events, such acute pancreatitis or cancer, and it is unlikely that randomized trials of GLP-1 agonists designed to detect malignancies will ever exist, clinicians should rely on observational studies in future assessment of the risk of cancer. A rigorous monitoring of these outcomes should be implemented in the future studies since current evidence

was not adequately designed to address this issue, precluding any definitive conclusion.

### Conflict of interest

All the authors declare to have no conflict of interest relevant to the subject matter or materials discussed in the article.

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Carlos Alves performed the electronic search, analyzed data, interpreted the results, contributed to the critical discussion and wrote the manuscript. Ana Filipa Macedo and Francisco Batel-Marques supervised data analysis, interpreted results, contributed to the critical discussion, reviewed and edited the manuscript. The opinion of Ana Filipa Macedo was requested in case of disagreement between Carlos Alves and Francisco Batel-Marques.

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### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.diabres.2012.09.008>.

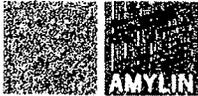
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# **EXHIBIT 3**



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19 May 2009

Mary H. Parks, MD, Director  
FDA/CDER  
Division of Metabolism and Endocrinology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Re: NDA 021-773** **Response to FDA Request**  
**BYETTA<sup>®</sup> (exenatide) injection** **for Information**  
**Serial 0217**

Dear Dr. Parks:

Reference is made to Amylin Pharmaceuticals, Inc. (Amylin) approved New Drug Application (NDA) 021-773 for BYETTA<sup>®</sup> (exenatide) injection. Reference is also made to the following:

- Email correspondences from you to Dawn Viveash, MD (Amylin), on 02 May and 03 May 2009, in which you posed various questions related to pancreatitis as well as patient drop-outs in the original NDA submission.

Amylin's response to your questions was emailed to the Agency on 08 May 2009, and the purpose of this submission is to provide the same response as a formal submission to the NDA.

Should you have questions regarding this submission, please contact Staci Ellis, Director, Regulatory Affairs at (858) 754-4903, or contact me, either by phone at (858) 309-7658 or by facsimile at (858) 625-0737.

Sincerely,

Dawn Viveash, MD  
Vice President, Regulatory Affairs and Safety

DV/hh

Confidential - Subject to Protective Order in JCCP 4574

Confidential - Subject to Protective Order in JCCP 4574  
BY00387461

Exhibit 3 - 69

In summary, the protocol-defined follow-up procedures would have enabled any event of pancreatitis occurring within the specified follow-up period to be brought to the sponsor's attention. No such cases were reported either for patients who were the subject of early discontinuation due to GI adverse events or for patients who were discontinued due to a serious adverse event of any nature.

**3. Please confirm that there were no cases of pancreatitis in the original NDA (clinical database) before approval.**

Two cases of pancreatitis were listed in the original BYETTA NDA (NDA 21-773) - 1 in a patient receiving exenatide and 1 in a patient receiving placebo. At the time of the 4-month safety update for NDA 21-773, an additional case was listed in an insulin glargine patient.

**4. In your Safety Amendment report you mentioned that as of 8/31/08, 4980 patients have participated in 41 clinical trials conducted by Amylin (or some similar language): 3331 received exenatide, 991 placebo, and 658 insulin. Can you provide the patient-yrs exposure for these data? Please also provide a breakdown of this database by exposure  $\geq$  24wks (or 6 mos),  $\geq$  52 wks (or 1 yr),  $\geq$  18 months.**

The table below provides the patient-yrs exposure data and a breakdown of this database by exposure, as requested for the data included within PSUR 007:

	Exenatide	Insulin	Placebo
	N=3331	N=658	N=991
	3065 yrs	397 yrs	374 yrs
<b>Number of Subjects with at least 24, 52, or 78 Weeks of Exposure</b>			
$\geq$ 24 weeks	n=1823 2733 yrs	n=459 341 yrs	n=417 235 yrs
$\geq$ 52 weeks	n=1070 2254 yrs	n=134 135 yrs	n=0
$\geq$ 78 weeks	n=645 1761 yrs	n=0	n=0

Data source: GIDB v3.1

Follow-up to the CHMP Pancreatic Cancer Review document, authored by Eli Lilly, dated 20 October 2008.

**5. 9 cases of pancreatitis have been reported in the cumulative postmarketing clinical trial database (Q4 above). I did not see any mention of necrotizing/hemorrhagic pancreatitis in this report. Can you confirm? Did you provide narratives of those 9 cases?**

Nine cases of pancreatitis were reported and included in the report referenced in Question 4 above. None of those patients had necrotizing and/or hemorrhagic pancreatitis. Currently, there are 11 pancreatitis cases in the clinical trial database,