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ORIGINAL RESEARCH

Pancreatitis Incidence in the Exenatide BID, Exenatide QW, and Exenatide QW Suspension Development Programs: Pooled Analysis of 35 Clinical Trials

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ABSTRACT

Introduction: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are widely used for treatment of type 2 diabetes mellitus; however, there have been concerns that GLP-1RA treatment may be associated with an increased incidence of pancreatitis. This study aimed to evaluate the incidence of pancreatitis in a pooled population of type 2 diabetes trials from the clinical development program of the GLP-1RA exenatide as well as to describe patient-level data for all reported cases.

Methods: The primary analysis examined pooled data among patients with type 2 diabetes from the controlled arms of 35 trials (ranging from 4 to 234 weeks' duration) in the integrated clinical databases for exenatide twice daily, once weekly, and once-weekly suspension, excluding comparator arms with other incretin-based therapies. The exposure-adjusted incidence rate (EAIR) of pancreatitis was calculated for exenatide and non-exenatide (non-incretin-based therapy or placebo) treatment groups. Patient-level data were described for all pancreatitis incidences.

Results: The primary analysis included 5596 patients who received exenatide and 4462 in the non-exenatide group. The mean duration of study medication exposure for the exenatide and non-exenatide treatment groups was 57.0 and 47.9 weeks, respectively. Pancreatitis was diagnosed in 14 patients (exenatide, $n = 8$; non-exenatide, $n = 6$), of whom 13 recovered with or without sequelae. The pancreatitis EAIR was 0.1195 events per 100 patient-years [95% confidence interval (CI), 0.0516–0.2154] in the exenatide group versus 0.1276 events per 100 patient-years (95% CI 0.0468–0.2482) in the non-exenatide treatment group. The EAIR ratio for the exenatide versus non-exenatide treatment group was 0.761 (95% CI 0.231–2.510).

Conclusion: In this pooled analysis of 10,058 patients among studies comparing exenatide

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with other glucose-lowering medications or placebo, pancreatitis was rare. The EAIRs of pancreatitis were low and similar between exenatide and non-exenatide treatment groups. No evidence of an association between exenatide and pancreatitis was observed.
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PLAIN LANGUAGE SUMMARY

Exenatide is a noninsulin injectable treatment for type 2 diabetes. There have been concerns about whether exenatide and other drugs that work in a similar way might be associated with increased risk of pancreatitis (inflammation of the pancreas). To assess new cases of pancreatitis occurring during treatment, we combined data from 35 clinical studies of exenatide in patients with type 2 diabetes. These studies included 5596 patients who received exenatide and 4462 patients who received placebo or a diabetes therapy that was unrelated to exenatide, in addition to their ongoing, usual treatment, for an average of about 1 year. The total treatment time (exposure) for exenatide across all 35 clinical trials was 6696 years. Fourteen patients developed pancreatitis (eight who had received exenatide and six who had received a different treatment). We provide details about each case of pancreatitis. After adjusting for different exposure times for each treatment, the number of new cases of pancreatitis expected to occur over 1 year was similar in patients treated with exenatide and those who received other unrelated treatments. We estimated that, for every 1000 patients who received exenatide or another treatment, we would expect to see 1.2 or 1.3 corresponding cases of pancreatitis per year, respectively. Our results were consistent with those from previous studies of pancreatitis in patients treated with exenatide or related therapies. In summary, our study found that pancreatitis occurred very rarely in patients treated with exenatide and at a similar rate as that in patients who received other treatments.

INTRODUCTION

Incretin-based therapies, including glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors, are widely used for the treatment of type 2 diabetes mellitus (T2DM). Exenatide, the first approved GLP-1RA, effectively improves glycemic control through enhanced glucose-dependent insulin secretion, inhibition of glucagon release, delayed gastric emptying, and weight loss induced by reduced food intake [1–4]. Since 2007, a number of postmarketing cases of acute pancreatitis have been reported with GLP-1RA treatment (including exenatide, liraglutide, and others) as well as with DPP-4 inhibitors, prompting the US Food and Drug Administration (FDA) to issue safety warnings about a possible temporal relationship between pancreatitis and agents in these classes [5–9]. Subsequent to these reports, all currently marketed GLP1-RA and DPP-4 inhibitors have label warnings regarding pancreatitis.

In 2013, the FDA and the European Medicines Agency independently conducted comprehensive evaluations of preclinical and clinical data submitted in support of marketing applications of incretin-based drugs and collected additional postmarketing safety data [10, 11]. Both the FDA and the European Medicines Agency concluded that the current data do not suggest an increased risk of pancreatitis events with incretin-based therapies but warned that pancreatitis would continue to be considered a risk associated with these therapies until additional definitive clinical and real-world data become available [10, 11].

Since that time, multiple studies have been conducted to investigate the potential relationship between incretin-based therapies—GLP-1RAs and DPP-4 inhibitors—and pancreatitis. Importantly, several long-term randomized controlled clinical trials to evaluate cardiovascular outcomes with GLP-1RAs and DPP-4 inhibitors were recently completed [12–18]. Most of these trials, including results of

EXSCEL (Exenatide Study of Cardiovascular Event Lowering; ClinicalTrials.gov identifier: NCT01144338) [12], adjudicated pancreatic events to enhance understanding of the risk of pancreatitis associated with incretin-based therapies.

The present study, which complements adjudicated data on pancreatic events from the EXSCEL trial, aimed to investigate the incidence of pancreatitis and review the clinical data associated with identified pancreatitis events using pooled data from 35 randomized trials across multiple exenatide formulations in the exenatide clinical development program. To account for differences in the duration of drug exposure, the exposure-adjusted incidence rate (EAIR) for pancreatitis, which provides a measure of the number of patients who had pancreatitis divided by the person-time at risk, was calculated for exenatide-treated and non-exenatide-treated patients. To better understand the nature of observed cases, patient-level data were compiled and reviewed for all cases of pancreatitis.

METHODS

Study Design

The primary analysis included integrated, pooled clinical data from 35 clinical trials for the exenatide twice daily (BID), once weekly (QW), and QW suspension programs that were completed before 2016. The analysis included randomized, placebo-, or active comparator-controlled phase 2/3 studies of exenatide used as monotherapy or add-on therapy to metformin, a sulfonylurea, a thiazolidinedione, or insulin for 4–234 weeks in patients with T2DM. Both double-blind and open-label studies were included; however, uncontrolled extension periods of studies were excluded. Studies with short exenatide exposure (defined as < 4 weeks) and studies conducted in healthy participants (e.g., patients without T2DM) were also excluded. In addition, GLP-1RAs other than exenatide and other incretin-based comparator therapies were excluded from the analysis. Two groups were analyzed: a group treated with exenatide and a non-exenatide group, which was treated with a non-incretin-based active comparator therapy or placebo. Detailed methodology and primary findings for each study included in this analysis have been previously published (Electronic Supplementary Material Table S1). In all studies, patients were followed up until study completion or early discontinuation from study treatment. Notably, for most studies, pancreatitis events were not adjudicated by an external review committee.

Statistical Analysis

Adverse events (AEs) and serious AEs were reported by study investigators, consistent with guidance from the International Conference on Harmonisation. AEs were coded based on the Medical Dictionary for Regulatory Activities (MedDRA) versions 16.0 and 17.0. Cases of pancreatitis in the exenatide program were identified through the following MedDRA preferred terms: "Pancreatitis," "Pancreatitis, acute," "Pancreatitis, chronic," "Pancreatitis haemorrhagic," "Pancreatic haemorrhage," "Pancreatitis necrotising," "Pancreatitis necrotizing," "Pancreatic necrosis," "Pancreatitis relapsing," "Pancreatic pseudocyst," "Pancreatic pseudocyst drainage," "Pancreatitic phlegmon," "Hereditary pancreatitis," "Ischaemic pancreatitis," "Oedematous pancreatitis," "Pancreatic abscess," "Pancreatorenal syndrome," and "Cullen's sign."

Descriptive statistics were provided for demographics and baseline variables. The duration of exposure was calculated using the time from first dose to last dose. The EAIR was calculated for pancreatitis events in the exenatide and non-exenatide groups. For EAIR calculations, exposure time was defined as the time to the first event, if an event occurred, or duration of drug exposure. The confidence interval (CI) of the EAIR was calculated from inverse gamma distribution assuming Poisson distribution for pancreatitis events. The ratio of EAIRs was computed from a Poisson regression weighted by the probabilities of receiving exenatide treatment in each individual study, known as the inverse probability of treatment

weighted estimator. The Poisson regression was estimated using a generalized estimating equation with study as a cluster variable and compound symmetry covariance structure to account for within-study correlations. Statistical analyses were performed using SAS (SAS Institute, Cary, NC, USA).

The power to detect a meaningful difference in incidence was limited by the low incidence of pancreatitis and short follow-up time in the study. For example, assuming that the background EAIR is 0.12 per 100 patient-years and patients treated with exenatide have twice the risk of pancreatitis than the comparator group (i.e., an EAIR ratio of 2, which is usually considered a large difference), to achieve 80% power for detecting this difference, a sample size of at least 39,208 patients with 0.5 years of follow-up or 5596 patients with > 3.5 years of follow-up in each treatment group would be needed for a one-sided type-1 error rate of 0.025. In our data, a sample size of 5596 patients (n for pooled exenatide patients) in each treatment group, with a median follow-up time of 0.5 years, will provide only 20% power for detecting an EAIR ratio of 2.0. The power calculation assumed a constant incidence rate over time and was conducted using Power Analysis and Sample Size 2008 software (NCSS, LLC, Kaysville, UT, USA).

Patient-level data were compiled and reviewed by the authors, including patient characteristics, pertinent medical history, risk factors associated with pancreatitis, concomitant medication use, biochemical findings such as lipase and amylase levels (where available), radiologic reports (where available), pancreatitis event latency, and outcomes and management.

Compliance with Ethics Guidelines

This study involves only analysis of previously published data and contains no new data from human participants. Therefore, informed consent and approval by an Institutional Ethics Committee were not required. All subjects consented, and ethics approvals were obtained for the original data collection as part of the original clinical trials.

RESULTS

Patient Demographics and Clinical Characteristics

Demographics and clinical characteristics were well balanced between patients who were treated with exenatide ($n = 5596$) and those in the non-exenatide group ($n = 4462$) (Table 1). Both groups were similar in terms of age, sex, duration of T2DM, body weight, body mass index, and glycated hemoglobin. Baseline blood pressure, serum triglycerides, and serum cholesterol concentrations were similar between groups. Use of concomitant medications that have been associated with the development of acute pancreatitis, including statins, angiotensin-converting enzyme inhibitors, calcium-channel blockers, and nonsteroidal anti-inflammatory drugs was also similar.

Duration of Exposure to Exenatide

Mean (minimum–maximum) exposure of study medication was 57.0 weeks (0.1–251.9 weeks) and 47.9 weeks (0.1–233.6 weeks) in the exenatide and non-exenatide treatment groups, respectively. Only 7.5% of exenatide-treated patients ($n = 422$) were exposed to exenatide for ≤ 30 days, while 30.6% ($n = 1714$) were exposed to exenatide for > 1 year. The total exposure to exenatide was 6696 years.

Incidence of Pancreatitis with Exenatide Versus Non-Exenatide Treatment

Pancreatitis was reported in 14 patients across the clinical development program [exenatide, $n = 8$ (0.14%); non-exenatide treatment, $n = 6$ (0.13%)] (Table 2). No patient reported > 1 pancreatitis event. Among exenatide-treated patients, five were treated with exenatide BID and three with exenatide QW. No cases of pancreatitis were reported in patients treated with exenatide QW suspension, although only 204 of the 5596 exenatide-treated patients received this formulation. In the non-exenatide group, patients with pancreatitis received

Table 1 Demographics and baseline clinical characteristics by exenatide use

Characteristic	Exenatide-treated patients (*n* = 5596)	Non-exenatide-treated patients[a] (*n* = 4462)
Age, years	56.0 ± 10.12	56.1 ± 9.95
Age category, *n* (%)		
< 65 years	4408 (78.8)	3508 (78.6)
≥ 65 years	1188 (21.2)	954 (21.4)
Male sex, *n* (%)	3122 (55.8)	2476 (55.5)
Region, *n* (%)		
North America	2325 (41.5)	1410 (31.6)
Other regions	3271 (58.5)	3052 (68.4)
Duration of type 2 diabetes, *n* (%)		
< 5 years	2071 (37.0)	1700 (38.1)
5–10 years	2018 (36.1)	1582 (35.5)
> 10 years	1362 (24.3)	1103 (24.7)
Not available	145 (2.6)	77 (1.7)
Body mass index, kg/m^2	31.8 ± 5.50	31.6 ± 5.25
Body weight, kg	90.1 ± 19.82	89.0 ± 19.00
HbA1c, %	(*n* = 5594)	(*n* = 4461)
	8.2 ± 1.03	8.2 ± 1.05
Systolic BP, mm Hg	131.8 ± 15.31	132.1 ± 15.70
Diastolic BP, mm Hg	79.2 ± 9.16	79.2 ± 9.17
Triglycerides, mg/dl	(*n* = 4562)	(*n* = 3689)
	192.5 ± 153.1	192.5 ± 161.9
LDL-C, mg/dl	(*n* = 4554)	(*n* = 3613)
	108.1 ± 35.91	108.1 ± 35.52
HDL-C, mg/dl	(*n* = 4598)	(*n* = 3667)
	46.3 ± 12.36	46.3 ± 12.36
Total cholesterol, mg/dl	(*n* = 4630)	(*n* = 3677)
	189.6 ± 42.18	189.6 ± 42.18
Concomitant medications, *n* (%)		
ACE inhibitors	1732 (31.0)	1354 (30.3)
Calcium-channel blockers	827 (14.8)	708 (15.9)
NSAIDs	1114 (19.9)	953 (21.4)
Statins	1666 (29.8)	1452 (32.5)

n is as reported in the column heading unless otherwise noted

Data are shown as the mean ± standard deviation unless otherwise noted

ACE angiotensin-converting enzyme, *BP* blood pressure, *HbA1c* glycated hemoglobin, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *NSAIDs* nonsteroidal anti-inflammatory drugs

[a] Non-glucagon-like peptide-1 receptor agonist comparator, non-dipeptidyl peptidase-4 inhibitor comparator, or placebo

placebo (*n* = 1), insulin (*n* = 2), a sulfonylurea (*n* = 1), or pioglitazone (*n* = 2).

The EAIR of pancreatitis was similar between the exenatide and non-exenatide groups [0.1195 events per 100 patient-years (95% CI 0.0516–0.2154) and 0.1276 events per 100 patient-years (95% CI 0.0468–0.2482), respectively], with an EAIR ratio of 0.761 (95% CI 0.231–2.510; *P* = 0.6535) (Table 2).

Table 2 Pancreatitis events

	Exenatide-treated patients (n = 5596)	Non-exenatide-treated patients[a] (n = 4462)
Number of events	8	6
Incidence, %[b]	0.14	0.13
Total exposure, years[c]	6696.0	4700.6
EAIR per 100 patient-years (95% CI), events	0.1195 (0.0516–0.2154)	0.1276 (0.0468–0.2482)
EAIR ratio (95% CI)[d]	0.761 (0.231–2.510) P = 0.6535	

CI confidence interval, *EAIR* exposure-adjusted incidence rate

[a] Non-glucagon-like peptide-1 receptor agonist comparator, non-dipeptidyl peptidase-4 inhibitor comparator, or placebo

[b] Incidence is the number of patients with event/number of patients

[c] Exposure is either the time to first event, if an event occurred, or duration of drug exposure

[d] The ratio of EAIRs was computed from a Poisson regression weighted by the probabilities of receiving exenatide treatment in each individual study (inverse probability of treatment weighted estimator). Poisson regression was estimated using a generalized estimating equation with study as a cluster variable and compound symmetry covariance structure to account for within-study correlations

Table 3 Summary of pancreatitis cases

	Exenatide-treated patients (n = 5596)	Non-exenatide-treated patients[a] (n = 4462)
Patients with event	8 (0.14)	6 (0.13)
Patients with serious event	5 (0.09)	5 (0.11)
Severity of event		
Mild	3 (0.05)	1 (0.02)
Moderate	4 (0.07)	2 (0.04)
Severe	1 (0.02)	3 (0.07)
Result of event		
Hospitalization	4 (0.07)	5 (0.11)
Study withdrawal	3 (0.05)	2 (0.04)
Death	0	0
Other	3 (0.05)	1 (0.02)
Outcome of event		
Resolved with or without sequelae	7 (0.13)	6 (0.13)
Event continuing at last assessment	1 (0.02)	0
Time to event, mean number of weeks (minimum–maximum)[b]	33.0 (8.0–110.3)	24.2 (1.3–105.7)

Data are shown as the n (%) unless otherwise noted

[a] Non-glucagon-like peptide-1 receptor agonist comparator, non-dipeptidyl peptidase-4 inhibitor comparator, or placebo

[b] Time to event is the time to first event since first dose date

Review of Pancreatitis Cases

Pancreatitis events ranged from mild to severe, and most events resolved with or without sequelae (Table 3). Four of the exenatide-treated patients and five of the non-exenatide-treated patients were hospitalized, and three and two patients, respectively, withdrew from the study. No deaths occurred. Ten of the 14 events were reported as serious AEs (n = 5 in each group). Four cases of pancreatitis were assessed by the investigator as study-drug related or possibly study-drug related (exenatide BID, n = 2; exenatide QW, n = 2). The mean time to pancreatitis was comparable between groups.

Details of each pancreatitis case are provided in Table 4. Of the 14 patients with a pancreatitis event, 13 had events that resolved with or without sequelae, and one had an ongoing event during the study period that was of mild

Table 4 Cases of pancreatitis in the exenatide clinical development program for the treatment of T2DM for both exenatide-treated and non-exenatide-treated patients

Case number and treatment	Sex/age/ race/BMI/ T2DM duration	Preferred/verbatim terms	Latency/duration, days	Serious AE/study drug-related/ intensity	Details of pancreatitis diagnosis	Additional case details	Treatment/ actions taken	Outcome
ExBID								
Case 1: ExBID 5 μg	Male/ 61 years/ White/ 31 kg/m^2/ unknown	Pancreatitis/pancreatitis	325/16	Yes/possibly/moderate	Episodic symptom: severe left-side epigastric abdominal pain CT scan showed evidence of acute pancreatitis Amylase: elevated on day of onset at local health center [360 U/l (normal range 25–120 U/l)][a], and at ED [pancreatic: 409 U/l (normal range 10–65 U/l); elevated 1 day after onset (pancreatic: 293 U/l)[b] and 2 days after onset (995 U/l (normal range 25–120 U/l)][a]; normal 8 days after onset (73 U/l)[b]	US (abdominal) showed no gallstones CT scan showed liver cirrhosis Relevant risk factors: use of ACE inhibitors, NSAIDs, and statins Other drugs: insulin, MET	Hospitalization Concomitant medication Study drug discontinuation and subsequent study withdrawal	Resolved with or without sequelae
Case 2: ExBID 10 μg	Male/ 63 years/ Black or African American/ 26 kg/m^2/ 5 years	Pancreatitis/pancreatic pseudocyst	158/> 454	No/no/mild	NR	Relevant risk factors: history of acute pancreatitis, alcohol abuse, use of ACE inhibitors and statins Other drugs: MET, SU	Concomitant medication	Event continuing at last assessment

Table 4 continued

Case number and treatment	Sex/age/ race/BMI/ T2DM duration	Preferred/verbatim terms	Latency/duration, days	Serious AE/study drug-related/ intensity	Details of pancreatitis diagnosis	Additional case details	Treatment/ actions taken	Outcome
Case 3: ExBID 5 μg	Male/ 63 years/ White/ 27 kg/m^2/ 15 years	Pancreatitis/acute pancreatitis	156/9	Yes/no/severe	Episodic symptoms: severe abdominal pain, nausea, vomiting, weakness CT scan showed peripancreatic inflammation with small amount of fluid in abdomen US of pancreas was normal Amylase[a]: elevated (4066 U/l)[b] on day of onset Lipase: elevated (15,319 U/l)[b] on day of onset	CT scan showed no sign of pancreatic phlegmon or abscess ERCP showed a long common channel of the common bile duct and the pancreatic duct without stones in the common bile duct Relevant risk factors: cholecystitis followed by cholecystectomy 3 weeks before pancreatitis event; hyperlipidemia; use of ACE inhibitors, CCBs, NSAIDs, and statins Other drugs: insulin, MET, SU	Hospitalization Concomitant medication	Resolved with or without sequelae
Case 4: ExBID 10 μg	Male/ 43 years/ White/ 31 kg/m^2/ 6 years	Pancreatitis/pancreatitis	56/9	No/no/mild	NR	Cholelithiasis on same day as pancreatitis onset (1396-day duration) Relevant risk factors: cholelithiasis; use of ACE inhibitors and NSAIDs Other drugs: MET	NR	Resolved with or without sequelae

Table 4 continued

Case number and treatment	Sex/age/ race/BMI/ T2DM duration	Preferred/verbatim terms	Latency/duration, days	Serious AE/study drug-related/ intensity	Details of pancreatitis diagnosis	Additional case details	Treatment/ actions taken	Outcome
Case 5: ExBID 5 μg	Male/ 62 years/ Asian/ 23 kg/m^2/ 5 years	Pancreatitis acute	175/8	Yes/yes/moderate	Episodic symptoms: epigastric pain, vomiting CT scan showed enlarged pancreas Amylase (total): elevated 1 day after onset [1429 U/l (normal range, 39–134 U/l)] and 3 days after onset [239 U/l (normal range 39–134 U/l)]	US showed enlarged gallbladder and gallstone MRCP showed gallstone and gallbladder wall thickening, suggesting cholecystitis Relevant risk factors: cholelithiasis, use of NSAIDs and statins Other drugs: insulin, MET, other antidiabetic medication, SU	Hospitalization Study withdrawal	Resolved with or without sequelae

Table 4 continued

Case number and treatment	Sex/age/ race/BMI/ T2DM duration	Preferred/verbatim terms	Latency/duration, days	Serious AE/study drug-related/ intensity	Details of pancreatitis diagnosis	Additional case details	Treatment/ actions taken	Outcome
ExQW								
Case 6: ExQW 2 mg	Female/ 52 years/ White/ 41 kg/m^2/ 7 years	Edematous pancreatitis/ edematous pancreatitis	130/79	Yes/yes/moderate	Elevated amylase and lipase (see below) occurred on day of onset; there were no other clinical signs and symptoms 7 days after onset there was continued elevated amylase and lipase, but no other clinical symptoms Amylase: elevated day of onset [pancreatic: 105 U/l (normal range 13–53 U/l)], 1 day after onset [total serum: 105 U/l (normal range 0–100 U/l)], and 7 days after onset (total serum: 107 U/l)[b] Lipase: elevated day of onset [255 U/l (normal range 0–60 U/l)] and 7 days after onset [91 U/l (normal range 0–60 U/l)]	12 days after onset, patient reported vomiting and umbilical pain radiating to the back CT scan 13 days after onset showed slightly hypodense aspect of the head of the pancreas without peripheral fat infiltration, which could indicate edematous pancreatitis Amylase: elevated 13 days after onset (total serum: 102 U/l)[b] Lipase: elevated 13 days after onset (127 U/l)[b] Relevant risk factors: dyslipidemia, use of statins Other drug: MET	Study withdrawal	Resolved with or without sequelae

Table 4 continued

Case number and treatment	Sex/age/ race/BMI/ T2DM duration	Preferred/verbatim terms	Latency/duration, days	Serious AE/study drug-related/ intensity	Details of pancreatitis diagnosis	Additional case details	Treatment/ actions taken	Outcome
Case 7: ExQW 2 mg	Female/ 59 years/ White/ 26 kg/m^2/ 18 years	Pancreatitis/acute pancreatitis	772/9	Yes/yes/moderate	Episodic symptom: mild epigastric pain Amylase (serum): elevated 2 days before onset [119 U/l (normal range 28–100 U/l)] Lipase: elevated 8 days before onset [76 U/l (normal range 0–60 U/l)]; elevated 1 day before onset [127 U/l (normal range < 60 U/l)]	US did not show any abnormalities Relevant risk factors: use of ACE inhibitors and statins Other drugs: MET, SU	Hospitalization	Resolved with or without sequelae
Case 8: ExQW 2 mg	Male/ 60 years/ White/ 38 kg/m^2/ 0 year	Pancreatic pseudocyst/pancreas pseudocyst	78/33	No/no/mild	Amylase (total): normal 7 days after onset [79 U/l (normal range 20–112 U/l)] Lipase: normal 7 days after onset [53 U/l (normal range 0–60 U/l)]	Relevant risk factor: use of statins	NR	Resolved with or without sequelae
Comparator								
Case 9: Placebo	Male/ 73 years/ White/ 35 kg/m^2/ 3 years	Pancreatitis acute/acute pancreatitis	18/9	Yes/no/severe	CT scan showed mild peripancreatic edema Amylase (serum): elevated (400 U/l)[b] on day of onset Lipase (serum): elevated (1038 U/l)[b] on day of onset	Relevant risk factors: prior pancreatitis; cholecystectomy; hypertriglyceridemia; use of ACE inhibitors, NSAIDs, and statins Other drugs: insulin, SU	Hospitalization Concomitant medication Study drug change	Resolved with or without sequelae

Table 4 continued

Case number and treatment	Sex/age/race/BMI/T2DM duration	Preferred/verbatim terms	Latency/duration, days	Serious AE/study drug-related/intensity	Details of pancreatitis diagnosis	Additional case details	Treatment/actions taken	Outcome
Case 10: Pioglitazone	Female/51 years/White/25 kg/m^2/1 year	Pancreatitis/pancreatitis	122/3	Yes/no/severe	Episodic symptoms: severe abdominal pain radiating to the back, vomiting CT scan showed mild inflammation adjacent to pancreas (possibly due to pancreatitis, peptic ulcer disease, or other inflammatory processes) and nonspecific, small pancreatic calcifications suggestive of chronic pancreatitis, with no obvious acute pancreatitis findings identified US showed no pancreatic abnormality or peripancreatic fluid collection, and no abnormal gallbladder findings Amylase[a]: elevated on day of onset [138 U/l (normal range 25–115 U/l)] Lipase: elevated on day of onset [166 U/l (normal range 22–51 U/l)]	Cholecystitis on same day as pancreatitis onset (38-day duration) with subsequent cholecystectomy Relevant risk factors: none known Other drugs: insulin, MET	Hospitalization	Resolved with or without sequelae

Table 4 continued

Case number and treatment	Sex/age/ race/BMI/ T2DM duration	Preferred/verbatim terms	Latency/duration, days	Serious AE/study drug-related/ intensity	Details of pancreatitis diagnosis	Additional case details	Treatment/ actions taken	Outcome
Case 11: Pioglitazone	Male/ 57 years/ other/ 36 kg/m^2/ 10 years	Necrotizing pancreatitis/pancreatitis necrotizing	17/101	Yes/no/severe	Episodic symptoms: severe diffuse abdominal pain, nausea, vomiting, diarrhea CT scan 2 days after onset showed 'necrotizing pancreatitis;" most of the pancreas was nonenhancing; no pancreatic pseudocyst or abscess was found MRI 2 days after onset showed ill-defined soft tissues surrounding the pancreas Amylase[a]: elevated [7263 U/l (200× ULN)][b] 1 day after onset and improved to 169 U/l[b] 7 days after onset Lipase: elevated (7310 U/l)[b] 1 day after onset and improved to 21 U/l[b] 7 days after onset	CT scan 6 days after onset revealed cholelithiasis and persistent moderately severe peripancreatic and retroperitoneal stranding, suggestive of ongoing pancreatitis CT-guided abdominal aspiration 20 days after onset revealed hemorrhagic pancreas with pancreatic necrosis CT scan 33 days after onset showed mass lesion most likely a pancreatic abscess Surgical debridement occurred 39 days post onset, followed by clinical improvement Amylase (total serum) elevated 18 days post-onset (367 U/l)[b] Lipase elevated 18 days post-onset (97 U/l)[b] Relevant risk factors: hyperlipidemia; use of ACE inhibitors Other drugs: insulin, MET	Hospitalization Study withdrawal Concomitant therapy	Resolved with or without sequelae

Table 4 continued

Case number and treatment	Sex/age/ race/BMI/ T2DM duration	Preferred/verbatim terms	Latency/duration, days	Serious AE/study drug-related/ intensity	Details of pancreatitis diagnosis	Additional case details	Treatment/ actions taken	Outcome
Case 12: SU	Female/ 54 years/ White/ 25 kg/m^2/ 11 years	Pancreatitis/pancreatitis	232/8	No/no/moderate	NR	Relevant risk factor: elevated triglycerides Other drug: MET	NR	Resolved with or without sequelae
Case 13: Insulin	Male/ 61 years/ White/ 30 kg/m^2/ 8 years	Pancreatitis acute/mild acute pancreatitis	9/4	Yes/no/mild	Episodic symptom: severe abdominal pain CT scan showed evidence of "acute pancreatitis, Balthazar grade A" Amylase[a]: slightly elevated (NR) on day of onset and elevated (268 U/l)[b] 5 days after onset	Relevant risk factors: 2 prior episodes of pancreatitis, cholecystectomy; use of CCBs Other drugs: MET, SU	Hospitalization Study withdrawal	Resolved with or without sequelae

Table 4 continued

Case number and treatment	Sex/age/ race/BMI/ T2DM duration	Preferred/verbatim terms	Latency/duration, days	Serious AE/study drug-related/ intensity	Details of pancreatitis diagnosis	Additional case details	Treatment/ actions taken	Outcome
Case 14 Insulin	Female/ 64 years/ White/ 39 kg/m^2/ 6 years	Pancreatitis/pancreatitis due to biliary obstruction	740/12	Yes/no/moderate	Episodic symptoms: abdominal pain, vomiting CT showed mild enlargement of the pancreas head and body, undilated bile ducts, boundary width of hepatocholedochus, and no obstruction at papilla Vateri Amylase (serum) elevated day of onset [2938 U/l (normal range 24–126 U/l)] Amylase (pancreatic): normal 17 days after onset [51 U/l (normal range 13–53 U/l)] Lipase: elevated level 17 days after onset [110 U/l (normal range 0–60 U/l)]	US showed dilatation of extra- and intrahepatic bile ducts, ductus choledochus was dilated to width of 13 mm Subsequent CT scan showed significant regression in US biliary duct findings Relevant risk factors: cholecystolithiasis treated by cholecystectomy, use of NSAIDs and statins Other drugs: MET	Hospitalization	Resolved with or without sequelae

ACE angiotensin-converting enzyme, *AE* adverse event, *BMI* body mass index, *CCB* calcium-channel blocker, *CT* computerized tomography, *ED* emergency department, *ERCP* endoscopic retrograde cholangiopancreatography, *ExBID* exenatide twice daily, *ExQW* exenatide once weekly, *MET* metformin, *MRCP* magnetic resonance cholangiopancreatography, *MRI* magnetic resonance imaging, *NR* not reported, *NSAID* nonsteroidal anti-inflammatory drug, *SU* sulfonylurea, *T2DM* type 2 diabetes mellitus, *ULN* upper limit of normal, *US* ultrasound

[a] Laboratory value from local laboratory, with no indication of whether amylase measurement is pancreatic, blood, serum, etc.

[b] Laboratory value from local laboratory, with no reference range reported

intensity and considered unrelated to the study drug. The time of event onset (latency) ranged from 9 to 772 days. For the 13 patients whose event resolved with or without sequelae, the duration of the pancreatitis events ranged from 3 to 101 days; nine patients had an event duration of < 14 days. Of the 14 patients with a pancreatitis event, 13 had > 1 risk factor for pancreatitis, including prior or concomitant treatment with a non-glucose-lowering therapy that is associated with increased risk of pancreatitis. Patients most commonly presented with abdominal pain, often accompanied by nausea. Eight patients had a history of cholecystitis, had prior cholecystectomy, or experienced cholelithiasis during the pancreatitis event. Diagnostic imaging results were available for ten patients (see Table 4 for details). Elevated amylase and lipase clinical laboratory measures were reported for ten and seven patients, respectively. No obvious differences in the case details were apparent between patients in the exenatide and non-exenatide groups.

DISCUSSION

In this pooled analysis of 10,058 patients with T2DM from 35 clinical trials in the exenatide clinical development program, few cases of pancreatitis were reported. Treatment with exenatide was not found to be associated with an increased risk of pancreatitis compared with placebo or non-incretin–based active comparator in this population.

These data show that 8 of 5596 patients (0.14%) treated with exenatide had pancreatitis, of whom seven recovered with or without sequelae. For most cases, the study drug was not discontinued. Approximately half the patients who developed pancreatitis had a history of gallbladder disease, and most had received therapy from ≥ 1 of the drug classes known to be associated with pancreatitis. Importantly, T2DM itself is associated with a risk of pancreatitis [19, 20].

The results of the current study add to multiple studies that had previously explored the potential relationship between incretin-based therapies and pancreatitis, including preclinical experiments [21–27]; retrospective cohort, case–control, population-based, and other observational analyses [28–42]; meta-analyses of clinical study results [43–51]; and, as discussed below, large cardiovascular outcomes trials [12–18].

Previous studies have examined data pooled across 19 randomized clinical trials (n = 5594) of exenatide BID [52] or eight phase 3 studies (n = 4328) of exenatide QW [53]. These studies reported EAIRs for pancreatitis that were not statistically significantly different between exenatide BID and comparator (0.27 vs. 0.18 events per 100 patient-years; risk difference, 0.09) or were comparable between exenatide QW and comparator (0.5 vs. 0.5 events per 100 patient-years); however, these studies did not examine individual cases of pancreatitis.

Similar findings to those reported in the current article were observed with pooled analyses of pancreatitis in the clinical development program of two other GLP-1RAs, liraglutide and dulaglutide [54, 55]. A post hoc analysis of 18 phase 2 and phase 3 randomized clinical trials of a total of 9016 patients treated with liraglutide (5021 patient-years of exposure), placebo (397 patient-years of exposure), or active comparator (1354 patient-years of exposure) reported eight cases of acute pancreatitis with liraglutide and one case with an active comparator (glimepiride) [54]. The EAIRs of acute pancreatitis were 0.16 and 0.07 cases per 100 patient-years with liraglutide and total active comparators, respectively. Recognized risk factors for pancreatitis were observed in 75% of the acute pancreatitis cases with liraglutide treatment. In an assessment of 6005 patients in nine phase 2 and 3 clinical trials of dulaglutide (3531 patient-years of exposure), EAIRs were 0.085 patients per 100 patient-years for dulaglutide, 0.352 patients per 100 patient-years for placebo, and 0.471 patients per 100 patient-years for sitagliptin [55]. Adjudication confirmed three cases of acute pancreatitis with dulaglutide, three cases with sitagliptin, and one case with placebo; no adjudicated cases of pancreatitis occurred in the exenatide, metformin, or insulin glargine comparator groups. In our analysis, exenatide- and non-exenatide-treated patients

had EAIRs of 0.12 and 0.13 events per 100 patient-years, respectively.

In four completed large, randomized, double-blind, placebo-controlled studies that investigated long-term cardiovascular safety of a GLP-1RA in patients with T2DM, no significant difference in the incidence of pancreatitis was found between the GLP-1RA and placebo groups [12, 16–18]. Notably, each of these studies had an independent committee that adjudicated all potential cases of pancreatitis. In the EXSCEL trial, in which 14,752 patients were randomized to receive exenatide QW or placebo and were followed up for a median of 3.2 years, the percentage of patients who experienced acute pancreatitis was low [0.4% (n = 26) for exenatide QW and 0.3% (n = 22) for placebo] [12, 56]. The EAIRs of confirmed acute pancreatitis in the EXSCEL trial were similar for exenatide QW (0.12 events per 100 patient-years) and placebo (0.10 events per 100 patient-years). In the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; ClinicalTrials.gov identifier: NCT01179048) trial of 9340 patients followed for 3.5–5 years, no statistically significant difference occurred in the percentage of patients who experienced acute pancreatitis between treatment groups [0.4% (n = 18) for liraglutide and 0.5% (n = 23) for placebo; P = 0.44] [18]. Furthermore, in LEADER the EAIRs for pancreatitis for patients treated with liraglutide or placebo were similar (0.11 or 0.17 events per 100 patient-years, respectively) [57]. The ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome; ClinicalTrials.gov identifier: NCT01147250) trial (n = 6068) demonstrated low and comparable percentages of confirmed pancreatitis events for patients treated with lixisenatide [0.2% (n = 5)] or placebo [0.3% (n = 8)], with mean durations of exposure of 690 and 712 days, respectively [16]. In SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; ClinicalTrials.gov identifier: NCT01720446), 3297 patients were randomized to receive semaglutide QW 0.5 mg, semaglutide QW 1.0 mg, or volume-matched placebo for 2 years. The percentage of patients with acute pancreatitis was similar between groups treated with semaglutide [0.5% (n = 9)] or placebo [0.7% (n = 12)] [17]. The currently ongoing cardiovascular outcomes trial for dulaglutide, REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes; ClinicalTrials.gov identifier: NCT01394952), will also adjudicate events of pancreatitis [58].

The results of the current study are consistent with recent meta-analyses of GLP-1RA clinical trials that do not observe an increased risk of pancreatitis with GLP-1RAs [59–62]. Conversely, three recent meta-analyses of randomized clinical trials of DPP-4 inhibitors reported an increased risk of acute pancreatitis. The first meta-analysis examined three prospective cardiovascular trials with 36,543 patients and reported an increased risk of acute pancreatitis with DPP-4 inhibitors [relative risk, 1.79 (95% CI 1.13–2.81)] [50]. The second meta-analysis examined 36 placebo-controlled studies with 54,664 patients and also found an increased risk of acute pancreatitis with DPP-4 inhibitors [relative risk, 1.57 (95% CI 1.03–2.39)] [51]. Finally, a meta-analysis of 38 randomized clinical trials including 59,404 patients reported an increased risk of acute pancreatitis with DPP-4 inhibitors compared with placebo or active comparators [Peto odds ratio, 1.72 (95% CI 1.18–2.53)] [63].

Several limitations were present in the current analysis. Patients had a relatively short exposure to exenatide, with most of the included studies having a duration of $\leq$ 6 months. Because many of these studies were conducted prior to the emergence of a potential pancreatic signal from postmarketing reports, limited confirmatory clinical data (e.g., amylase and lipase concentrations, imaging results) were available, detailed information on potential risk factors for pancreatitis (e.g., alcohol and tobacco use) was not collected, and pancreatic events were not formally adjudicated. As pancreatitis was a rare event, the integrated database that was used in the present study may not have been sufficiently large to investigate events of pancreatitis. Although the duration of the studies in the current analysis was limited, subsequently conducted long-term clinical trials and meta-analyses also have reported low

incidences of pancreatitis [12, 16–18, 57, 59–61], and long-term data (up to 6 years) from the uncontrolled extension of DURATION-1 (n = 136) suggest a very low risk of pancreatitis, with only one case reported (EAIR of 0.1 event per 100 patient-years) [64].

CONCLUSION

In this pooled analysis from 35 trials (4–234 weeks' duration) in the exenatide clinical development program, pancreatitis events were very rare. The incidence of pancreatitis was similar among exenatide-treated patients and those who were treated with placebo or a non-incretin-based active comparator, and demographics and baseline characteristics were similar between groups. Results from this study are consistent with findings from both large observational studies that mostly suggest there is no increased risk of pancreatitis associated with exenatide and from large cardiovascular outcome trials and meta-analyses that do not report an increased risk of pancreatitis with GLP-1RAs. Although cases of pancreatitis in the exenatide clinical development program were rare, physicians should remain vigilant in monitoring for symptoms indicative of pancreatitis [65, 66].

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Compliance with Ethics Guidelines. This study involves only analysis of previously published data and contains no new data from human participants. Therefore, informed consent and approval by an Institutional Ethics Committee was not required. All subjects consented and ethics approvals were obtained for the original data collection as part of the original clinical trials.

Data Availability. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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