Assessment of Pancreas Safety in the Development Program of Once-Weekly GLP-1 Receptor Agonist Dulaglutide

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OBJECTIVE

To assess the risk of acute pancreatitis during treatment with glucagon-like peptide 1 receptor agonist dulaglutide, placebo, and active comparators across phase 2/3 dulaglutide trials.

RESEARCH DESIGN AND METHODS

A total of 6,005 patients with type 2 diabetes participated (dulaglutide group *N* = 4,006 [dose range 0.1–3.0 mg]; active comparator group [metformin, sitagliptin, exenatide twice daily, insulin glargine] *N* = 1,541; placebo group *N* = 703; 245 placebo-treated patients subsequently received dulaglutide or sitagliptin and were also included in these groups) for up to 104 weeks. The following events were adjudicated: investigator-reported pancreatitis, adverse events (AEs) of severe or serious abdominal pain of unknown etiology, and confirmed asymptomatic increases in pancreatic enzymes ≥3× the upper limit of normal range.

RESULTS

Overall, 203 events from 151 patients underwent adjudication (dulaglutide group *n* = 108; comparator group including placebo *n* = 43). Acute pancreatitis was confirmed by adjudication in seven patients (dulaglutide *n* = 3, placebo *n* = 1, sitagliptin *n* = 3). Exposure-adjusted incidence rates were as follows: dulaglutide group 0.85 patients/1,000 patient-years, placebo group 3.52 patients/1,000 patient-years, sitagliptin group 4.71 patients/1,000 patient-years. No events of pancreatitis were confirmed by adjudication in patients treated with exenatide twice daily, metformin, or glargine. Increases in median values of lipase and pancreatic amylase within the normal range were observed with all treatments except glargine. These changes were not associated with AEs.

CONCLUSIONS

The exposure-adjusted incidence rate of acute pancreatitis in dulaglutide-treated patients was similar to the rates with placebo, with few reported cases during the entire program.

Glucagon-like peptide 1 (GLP-1) receptor agonists are used for the treatment of type 2 diabetes because of their clinically relevant glucose-lowering effects, low risk of hypoglycemia, and beneficial effects on weight (1–3). Treatment with GLP-1 receptor agonists is associated with an increased incidence of gastrointestinal adverse events, which are mostly mild to moderate in intensity (4). After the

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introduction of the first GLP-1 receptor agonist, exenatide twice daily, rare cases of potentially drug-related pancreatitis were reported, which led regulators and pharmaceutical manufacturers to further evaluate the risk of pancreatitis with the use of the GLP-1 receptor agonist class (2,3). Most of the retrospective epidemiological reports did not indicate increased reporting of acute pancreatitis with exenatide and/or liraglutide; however, some have suggested (5–13) a potential increased incidence with these agents or with incretin-based therapies in general. Because of conflicting results and multiple confounding factors that are often poorly controlled for in retrospective studies, the relevance of these reports is limited (7,8,14,15). Recently, prospective, controlled data have become available from development programs of various GLP-1 receptor agonists (16). A pooled analysis of data available for exenatide, liraglutide, and lixisenatide showed more frequent reporting of acute pancreatitis with these agents versus comparators, but the difference was not statistically significant (17). These results should also be considered with caution since the exposure to GLP-1 receptor agonists and other glucose-lowering agents included in these studies was short and the number of reported outcomes was low. Acute pancreatitis generally has a very low incidence in the population, and evaluation of the risk in a specific subpopulation requires a larger sample size and longer exposure. Therefore, collecting more data related to the pancreas safety in patients treated with these agents is needed. It is reassuring that no changes have been observed in various nondiabetic and diabetic animal models during long-term exposure to GLP-1–based therapeutics (18).

Dulaglutide is a once-weekly GLP-1 receptor agonist recently approved for the treatment of type 2 diabetes (19). During the dulaglutide development program, the incidence of acute pancreatitis was assessed based on the safety reporting of adverse events by the investigative sites and through a prospective screening process applied to the entire patient population included in the program. Several categories of adverse events or other clinical findings were adjudicated to verify the presence of acute or chronic pancreatitis. The results of the assessment are presented in this report, along with other clinical observations that may be of importance for characterizing the effects of dulaglutide on the exocrine pancreas.

RESEARCH DESIGN AND METHODS

The dulaglutide registration clinical trial program included four phase 2 trials (trials 1–4) and five phase 3 confirmatory trials (AWARD [Assessment of Weekly Administration of LY2189265 [dulaglutide] in Diabetes] 1–5). Study designs of the trials have been published previously (16,20–23). Patients with a medical history of acute or chronic pancreatitis, as assessed by the investigators, were excluded from all trials. Dulaglutide was compared with placebo (six trials) and active comparators, including metformin, sitagliptin, exenatide, and insulin glargine (two trials). The duration of treatment ranged from 12 to 26 weeks in phase 2 trials 1–4 and from 52 to 104 weeks in the phase 3 AWARD 1–5 trials. Two AWARD trials included placebo arms up to 26 weeks and then switched these participants in a blinded manner to dulaglutide (AWARD-1) or to sitagliptin (AWARD-5). In phase 2 trials 1–4, patients were exposed to doses ranging from 0.1 mg to 3.0 mg. The final doses selected for AWARD trials were 1.5 and 0.75 mg (24) and were the most commonly used doses overall. In most of the trials, patients were allowed to continue in the study after the introduction of additional (or rescue) glucose-lowering intervention or discontinuation of the study drug for any reason. Each trial was conducted in accordance with the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines, the International Conference on Harmonization Good Clinical Practices Guideline, and all other applicable laws and regulations. All participants provided written consent prior to undergoing any procedure.

The following events of interest were prespecified: *1*) investigator-reported adverse events of pancreatitis; *2*) adverse events of severe and/or serious abdominal pain without known etiology; and *3*) asymptomatic, clinically relevant increases in concentration of one or more pancreatic enzymes (lipase, total amylase, pancreatic amylase) defined as values $\geq 3\times$ upper limit of normal range (ULN), confirmed by a repeat test (Supplementary Fig. 1). To search for cases of asymptomatic, clinically relevant increases in pancreatic enzymes, serial enzyme measurements were performed at screening, baseline, and during treatment at weeks 2–4, 8–16, 26, 39, 52, and 78–104, depending on study design and duration. The purpose of the serial assessments was to screen for possible subclinical changes in the pancreas irrespective of etiology (inflammatory or noninflammatory) and to initiate further diagnostic assessment to determine whether signs of structural abnormalities could be detected in the exocrine pancreas. Patients with this finding were subject to a structured diagnostic workup using an algorithm that included abdominal imaging (computed tomography or MRI) (Supplementary Fig. 1).

The Duke Clinical Research Institute Clinical Event Classification Group (CEC), which consisted of board-certified physicians with expertise in the field of gastroenterology and prior CEC experience (Duke University Medical Center, Durham, NC), served as an independent end point committee for blinded adjudication. The pancreatic events of interest were submitted to the CEC starting in October 2009, ~16 months after the beginning of the first phase 3 trial, and continued until the completion of all studies included in the assessment. The sponsor, the investigative sites, and the CEC were blinded throughout the process. A patient may have had more than one event, and each event was assessed separately. Events were adjudicated as confirmed pancreatitis, not confirmed (ruled out), or unknown if pancreatitis (equivocal). Events of confirmed pancreatitis were further classified as acute, chronic, or unknown type (i.e., indeterminate: events that may have met the definition of pancreatitis but were unable to be classified as either acute or chronic) by the committee. Two of the following three criteria were required for an event to be adjudicated as confirmed acute pancreatitis: *1*) severe upper abdominal pain, *2*) serum amylase and/or lipase level $\geq 3\times$ ULN, and *3*) imaging results that indicated inflammatory changes in the pancreatic parenchyma (25,26). A total of five potentially qualifying events (2.4% of 208) were missed by the sites to be assessed and submitted to the CEC for adjudication. Retrospective adjudication was not possible due to incomplete information. The proportion of these events was balanced

across treatments (dulaglutide 1.5 mg n = 1; dulaglutide 0.75 mg n = 1; insulin glargine n = 1; metformin n = 2). Additional details related to the adjudication process are provided in the Supplementary Appendix.

All blood samples were analyzed by a central laboratory (Quintiles Laboratories Europe, West Lothian, U.K.). Normal laboratory ranges used as reference limits when evaluating pancreatic enzymes were 0–60 units/L for lipase, 13–53 units/L for pancreatic amylase (p-amylase), and 20–112 units/L for total amylase. Measurements of pancreatic amylase were not collected in two of the phase 2 trials, and the collection of total amylase in AWARD-5 was implemented after the start of the study. Other laboratory tests performed in the event of suspected acute pancreatitis included testing hepatic functional parameters, triglycerides, complete blood count, and/or calcium.

Statistical Analysis

Pancreatitis events are presented as determined by adjudication; events as reported by the investigator are tabulated in Table 2. Summaries include all events observed at any time, including any events observed at a safety follow-up visit 30 days after the cessation of treatment. The total number of patient-years (PY) of study drug exposure differed between the various treatments in the nine studies; in addition to counts, exposure-adjusted rates (per 1,000 PY of study drug exposure) are presented.

Pancreatic enzymes are presented by study as proportions of abnormal maximum values (thresholds $\geq$2$\times$ ULN and $\geq$3$\times$ ULN) through 26 weeks. The Supplementary Appendix includes screening and baseline values as boxplots by study, and postbaseline data for dulaglutide 0.75 mg and dulaglutide 1.5 mg in studies of at least 1 year in duration are presented as a time course from baseline through 1 year of treatment (median with 5th and 95th quantiles). Only data for lipase and p-amylase are presented, since changes for total amylase were generally smaller in magnitude compared with changes in p-amylase, suggesting greater sensitivity of the latter for shifts observed after the initiation of a new treatment intervention.

RESULTS

Exposure to Study Drug

The population for this integrated assessment of nine phase 2 and 3 dulaglutide trials included 6,005 randomized patients who received at least one dose of study drug (dulaglutide, placebo, or active comparators), with a total 5,537 PY of study drug exposure. Of these patients, 4,006 received dulaglutide (3,531 PY), 703 received placebo (284 PY), and 1,541 received active comparator (1,722 PY). By design, a small number of patients received 26 weeks of placebo followed by an active therapy (dulaglutide N = 121; sitagliptin N = 124) and are included in the totals of subjects exposed for each therapy received. There were 2,821 patients who received dulaglutide for $\geq$26 weeks, 1,595 patients who received dulaglutide for $\geq$52 weeks, and 157 patients who received dulaglutide for $\geq$104 weeks. The patients' baseline characteristics are summarized in Supplementary Table 1.

Adjudicated Events of Treatment-Emergent Pancreatitis

A total of 203 individual events from 151 patients (patients who received dulaglutide n = 108; patients who received active comparator and placebo but were not exposed to dulaglutide n = 43; Table 1) underwent pancreatic adjudication in the program. Of these events, 19 were reported by investigators as treatment-emergent adverse events of pancreatitis. Other cases encompassed clinical findings that met other prespecified criteria for adjudication (confirmed hyperenzymemia or serious or severe abdominal pain of unknown etiology per the definitions from the Medical Dictionary for Regulatory Activities Preferred Terms) (27). Seven events of acute pancreatitis were confirmed by adjudication (patients who received dulaglutide n = 3, patients who received sitagliptin n = 3, and patients who received placebo n = 1). One of these cases that occurred in a patient treated with dulaglutide was adjudicated as pancreatitis, but the type of event could not be determined. We included this event in the category of acute pancreatitis for data presentation. Exposure-adjusted incidence rates of these events for each type of treatment are provided in Table 1. Incidence rates with dulaglutide treatment were numerically lower than those with placebo and sitagliptin treatment (Table 1). No event submitted to the adjudication committee for patients treated with exenatide, metformin, or insulin glargine met the criteria for acute pancreatitis. Table 2 summarizes incidence rates for all cases of adjudicated pancreatitis (overall, acute, chronic, or indeterminate type), as well as the incidence rate for events reported by the investigative sites as pancreatitis (i.e., before adjudication).

Supplementary Table 2 provides the clinical characteristics of patients adjudicated with acute or chronic pancreatitis including initial clinical findings that triggered evaluation. Of the five pancreatitis

Table 1—Outcome of adjudication of cases of interest in treatment groups included in the dulaglutide development program

Treatment arm[a]	N	Years of exposure (PY)	Patients with adjudications performed		Adjudicated cases confirmed as acute pancreatitis	
			n (%)	n/1,000 PY	n (%)	n/1,000 PY
Dulaglutide[b]	4,006	3,531	108 (2.7)	30.6	3 (<0.1)	0.85
Placebo	703	284	8 (1.1)	28.2	1 (0.1)	3.52
Metformin	268	227	4 (1.5)	17.6	0 (0.0)	0
Sitagliptin	439	637	11 (2.5)	17.3	3 (0.7)	4.71
Exenatide	276	236	7 (2.5)	29.6	0 (0.0)	0
Insulin glargine	558	621	13 (2.3)	20.9	0 (0.0)	0

[a]By design, a small number of patients received 26 weeks of placebo followed by an active therapy (dulaglutide, N = 121; sitagliptin, N = 124). These patients are included in totals of subjects exposed for each therapy received (throughout the article). [b]One of these three events was classified as Pancreatitis, Indeterminate Type by the adjudication committee. This event, occurring in a dulaglutide patient, is conservatively categorized as Acute Pancreatitis for purpose of analysis.

Table 2—Exposure-adjusted incidence of treatment-emergent pancreatitis as adjudicated and as reported by investigators

	Events of pancreatitis confirmed by adjudication or equivocal results of adjudication		Events of pancreatitis as reported by investigators	
	n (%)	*n*/1,000 PY	*n* (%)	*n*/1,000 PY
Dulaglutide, *N* = 4,006		Years of exposure (3,531 PY)		Years of exposure (3,531 PY)
Pancreatitis, any type	5 (0.1)	1.42	12 (0.3)	3.40
Pancreatitis, acute	2 (<0.1)	0.57		
Pancreatitis, chronic	2 (<0.1)	0.57		
Pancreatitis, indeterminate type[a]	1 (<0.1)	0.28		
Pancreatitis, equivocal diagnosis[b]	3 (<0.1)	0.85		
Placebo comparator, *N* = 703		Years of exposure (284 PY)		Years of exposure (284 PY)
Pancreatitis, any type	1 (0.1)	3.52	1 (0.1)	3.52
Pancreatitis, acute	1 (0.1)	3.52		
Pancreatitis, equivocal diagnosis[b]	0 (0.0)	0		
Active comparator				
Metformin, *N* = 268		Years of exposure (227 PY)		Years of exposure (227 PY)
Pancreatitis, any type	0 (0.0)	0	0 (0.0)	0
Pancreatitis, equivocal diagnosis[b]	0 (0.0)	0		
Sitagliptin, *N* = 439		Years of exposure (637 PY)		Years of exposure (637 PY)
Pancreatitis, any type	3 (0.7)	4.71	3 (0.7)	4.71
Pancreatitis, acute	3 (0.7)	4.71		
Pancreatitis, equivocal diagnosis[b]	0 (0.0)	0		
Exenatide, *N* = 276		Years of exposure (236 PY)		Years of exposure (236 PY)
Pancreatitis, any type	0 (0.0)	0	1 (0.4)	4.23
Pancreatitis, equivocal diagnosis[b]	0 (0.0)	0		
Insulin glargine, *N* = 558		Years of exposure (621 PY)		Years of exposure (621 PY)
Pancreatitis, any type	0 (0.0)	0	2 (0.4)	3.22
Pancreatitis, equivocal diagnosis[b]	1 (0.2)	1.61		

[a]Adjudication review confirms pancreatitis = yes and type of pancreatitis = unknown. [b]Adjudication review confirms pancreatitis = unknown.

events diagnosed in dulaglutide-treated patients, two were acute, two were chronic, and for one patient the type of event could not be determined with certainty. All five patients had elevated pancreatic enzyme levels prior to exposure to the study drug. The assessment of risk factors for acute pancreatitis showed that one of these patients had cholelithiasis (microlithiasis in the gallbladder). For patients with acute pancreatitis, there were no distinct or consistent clinical features with respect to clinical presentation, duration of exposure to dulaglutide or the comparator, or clinical course.

Table 3 summarizes the data for patients with adjudicated events, including events "equivocal if pancreatitis" or "pancreatitis ruled out" (including all cases of investigator-reported pancreatitis in these categories). The number of patients who presented with some signs and/or symptoms that, however, did not meet the criteria for the diagnosis of acute pancreatitis was small across the groups (patients who received dulaglutide 10, patients who received placebo 1, patients who received metformin 1, patients who received glargine 1, patients who received nonincretin comparators 3, patients who received sitagliptin 2, patients who received exenatide 1). Most of these patients already had asymptomatic pancreatic enzyme elevations at baseline. There were no relevant numerical differences between patients who received dulaglutide and patients who received placebo or active comparators for these cases.

Pancreatic Enzymes at Screening/Baseline and Changes Throughout Treatment Periods

The median values of lipase and p-amylase prior to randomization were similarly distributed across treatment groups and were within the reference range in each study (Supplementary Fig. 2). A proportion of patients had values above the ULN already at baseline (for lipase values: ≥2× ULN values ranged from 0.7% to 7.3%, ≥3× ULN values ranged from 0% to 4.0%; for p-amylase: ≥2× ULN ranged from 0% to 4.0%, ≥3× ULN ranged from 0% to 1.5%).

During the treatment period, median changes in lipase and p-amylase concentration for placebo in the placebo-controlled trials ranged from −2.0 to 1.5 and 0 units/L, respectively, at the last observation during treatment period (12–26 weeks) (Supplementary Table 3). Changes for these enzymes were greater with dulaglutide, and the effect of dulaglutide was dose dependent. The median changes for lipase ranged from 3.0 to 6.0 units/L for dulaglutide 0.75 mg and from 5.0 to 7.0 units/L for dulaglutide 1.5 mg. Corresponding changes for p-amylase were slightly smaller. This upward shift in the median values of pancreatic enzymes with dulaglutide treatment was associated with a greater proportion of patients reporting values ≥2× ULN and ≥3× ULN versus placebo for both enzymes (Table 4). At last visit, 4 weeks after the discontinuation of dulaglutide (safety follow-up visit), observed pancreatic enzymes had returned to near baseline levels (Supplementary Table 4).

Supplementary Fig. 3 also presents changes from baseline with dulaglutide 1.5 mg, dulaglutide 0.75 mg, placebo, and active comparators during the treatment period in phase 3 AWARD trials. In addition to the changes observed with the dulaglutide doses described above, upward shifts in median values for lipase were observed with exenatide, sitagliptin,

Table 3—Summary of all pancreatic events by treatment group

	Dulaglutide	Placebo	Metformin	Insulin glargine	All nonincretin comparators[e]	Sitagliptin	Exenatide
All randomized patients[a]	4,006 (100.0)	703 (100.0)	268 (100.0)	558 (100.0)	1,529 (100.0)	439 (100.0)	276 (100.0)
Patient exposure, PY[a]	3,531	284	227	637	1,148	637	236
Patients assessed for AP or CP	114 (2.8)	14 (2.0)	4 (1.5)	12 (2.2)	30 (2.0)	12 (2.7)	7 (2.5)
Patients adjudicated as AP or CP	5 (0.12)	1 (0.14)			1 (0.07)	3 (0.68)	
Patients adjudicated as equivocal AP	2 (0.05)			1 (0.18)	1 (0.07)		
Patients adjudicated as equivocal CP	1 (0.02)						
Patients adjudicated as pancreatitis ruled out	106 (2.6)	13 (1.8)	4 (1.5)	11 (2.0)	28 (1.8)	9 (2.1)	7 (2.5)
One clinical criterion[b] for AP met, other nondiagnostic signs or symptoms present[d]	10 (0.25)	1 (0.14)	1 (0.37)	1 (0.18)	3 (0.20)	2 (0.46)	1 (0.36)
Patients with abdominal pain and enzymes ≥3× ULN	10 (0.25)	1 (0.14)	1 (0.37)	1 (0.18)	3 (0.20)	2 (0.46)	1 (0.36)
One clinical criterion[c] for CP met, other nondiagnostic signs or symptoms present[d]	2 (0.05)			2 (0.36)	2 (0.13)		
One clinical criterion met, other nondiagnostic signs or symptoms absent[d]	94 (2.3)	12 (1.7)	3 (1.1)	8 (1.4)	23 (1.5)	7 (1.6)	6 (2.2)
Events assessed for pancreatitis, *N*	138	20	4	14	38	18	8
Events with data available for 3 clinical criteria	117	20	2	14	36	18	7
Events with data available for 2 clinical criteria	21	3	2		5		1
Events with data available for 1 clinical criterion							

Data are presented as *n* (%) unless otherwise indicated. AP includes cases of indeterminate type. AP, acute pancreatitis; CP, chronic pancreatitis. [a]Patients who received more than one treatment regimen (placebo and dulaglutide, or placebo and sitagliptin) were included in both groups; outcomes were attributed to the regimen patients were receiving at the time of onset. [b]Abdominal pain typical for acute pancreatitis, pancreatic enzymes ≥3× ULN, or positive abdominal imaging. [c]Abdominal pain, attacks of acute pancreatitis, diarrhea, weight loss, steatorrhea or complications of chronic pancreatitis, and positive abdominal imaging. [d]Atypical pain, enzymes >1× ULN and <3× ULN, and/or inconclusive results of abdominal imaging. [e]Placebo, metformin, and insulin glargine.

and metformin. The smallest changes were noted with insulin glargine. The changes were greatest with dulaglutide 1.5 mg versus all comparators, whereas dulaglutide 0.75 mg was associated with similar changes to exenatide and sitagliptin and greater changes compared with metformin or insulin glargine. Consistent with these observations was an increase in the proportion of patients with values ≥2× ULN and ≥3× ULN after a similar duration of exposure (at 26 weeks) (Table 4).

Other Pancreatic Events

Two dulaglutide-treated patients reported pancreatic cancer (<0.1%, 0.57/1,000 PY). One patient had a large, 5-cm tumor found within days of their first and only dose of dulaglutide 0.75 mg. This tumor was considered to have preexisted before initiation of treatment with the study drug. The other patient, treated with dulaglutide 1.5 mg, reported cramping abdominal pain in the left upper quadrant radiating into their back ~4 months after beginning to receive the study drug. Pancreatic enzyme levels were within the normal range; however, a month later a computed tomography scan revealed a mass covering the majority of the pancreas. Given the short duration the patient received the study drug, it was considered highly likely that the tumor was preexisting. No cases of pancreatic cancer were reported in the placebo group or in any comparator group.

CONCLUSIONS

We presented the results of the assessment of the incidence of acute pancreatitis and other observations relevant for understanding the effects of treatment with dulaglutide, a once-weekly GLP-1 receptor agonist, and various comparators on the exocrine pancreas. The number of cases of acute pancreatitis confirmed by adjudication in the overall patient population in the dulaglutide development program was low. The incidence rates with dulaglutide were numerically lower than the incidence rates observed with placebo. Most of the glucose-lowering medications that we studied, including dulaglutide, exenatide, sitagliptin, and, potentially, metformin, were associated with asymptomatic median increases in the concentration of pancreatic enzymes that were within the normal range, the clinical relevance of which remains uncertain.

Reported cases of pancreatitis with exenatide and liraglutide, and the potential causal relationship with these compounds is of a significant concern for patients and physicians when assessing benefit/risk relationships for various glucose-lowering agents (28,29). Prospective clinical research and safety surveillance is of great importance since the supporting experimental and mechanistic data are lacking, and the retrospective epidemiological studies reported in the literature have significant limitations (7,8,14,15). Because of a very low incidence of pancreatitis in the general population, pooling data from multiple prospective studies is needed to obtain meaningful results. The dulaglutide development program provided an opportunity to evaluate a large database, consisting of nine phase 2 and phase 3 trials with >6,000 participants, to assess the incidence of the pancreatic adverse events of interest, the effectiveness of screening procedures, and subclinical changes in the pancreas and their possible clinical relevance. The program included a set of procedures, such as the regular measurement of pancreatic enzymes and the use of a structured algorithm for the clinical assessment of patients, to prospectively collect comprehensive information on the risk of

Table 4—Summary of abnormal (≥2× ULN, ≥3× ULN) postbaseline pancreatic enzymes through 26 weeks

		Proportions of patients with values above the threshold[ab]							
		≥2× ULN (%)				≥3× ULN (%)			
Study	Comparator	DU 1.5 mg	DU 0.75 mg	AC	PL	DU 1.5 mg	DU 0.75 mg	AC	PL
Lipase									
AWARD-3	Metformin	6.8	6.7	6.0		4.9	2.6	1.9	
AWARD-5	Sitagliptin	14.6	15.1	12.1	11.9	6.3	7.0	6.4	6.3
AWARD-1	Exenatide	9.8	10.5	8.5	8.6	6.2	5.1	4.4	3.6
AWARD-2	Insulin glargine	18.1	15.2	7.3		11.4	5.9	4.2	
AWARD-4	Insulin glargine	7.7	7.1	4.9		2.5	2.5	1.7	
p-Amylase									
AWARD-3	Metformin	3.4	1.1	0.7		1.5	0	0.7	
AWARD-5	Sitagliptin	4.0	3.0	3.2	3.4	0.7	0.3	0.3	0.6
AWARD-1	Exenatide	4.0	4.0	2.2	2.2	1.5	0.7	0.4	0
AWARD-2	Insulin glargine	10.3	5.6	3.5		4.1	2.2	1.5	
AWARD-4	Insulin glargine	2.8	2.1	1.0		0.4	1.1	0.3	

AC, active comparator; DU, dulaglutide; PL, placebo. [a]Dulaglutide and active comparators in phase 3 studies, Threshold assessed using maximum postbaseline value through 26 weeks visit. [b]Percentages based on the number of patients with data (i.e., the number of patients with postbaseline laboratory test available).

pancreatitis and the overall safety of the pancreas.

The incidence of acute pancreatitis in the trials in this current assessment was low, with seven cases of adjudicated acute pancreatitis reported, three of them in patients treated with dulaglutide. Because of significant heterogeneity between trial populations, we summarized the incidence rates of acute pancreatitis for treatment with dulaglutide and for treatment with individual comparators from these trials. The placebo comparator was the most relevant because it should reflect the underlying risk of acute pancreatitis in the population included in the placebo-controlled trials and because placebo was the most common comparator in the program. The numerical estimate of the incidence of acute pancreatitis with dulaglutide treatment was lower compared with placebo. Comparisons to other comparators in the development program are of limited relevance because even fewer patients were exposed to these other agents. The low proportion of cases of confirmed pancreatitis versus the total number of adjudicated cases in dulaglutide-treated patients and with other treatments, except sitagliptin, reflects a frequent occurrence of mild, transient, asymptomatic increases in pancreatic enzymes with normal pancreatic imaging in patients with type 2 diabetes. There is no clear explanation for the higher proportion of confirmed cases with sitagliptin, but for more appropriate assessment of this risk, we refer to much larger databases with data on dipeptidyl peptidase 4 inhibitors (30) and a recent meta-analysis (31) of three cardiovascular outcomes trials using dipeptidyl peptidase 4 inhibitors, which showed a slightly elevated risk.

Of the seven cases of acute pancreatitis confirmed by adjudication in the program, five were diagnosed initially by the investigators as acute pancreatitis, whereas two patients initially presented with elevations in enzyme levels. We did not observe any distinct clinical pattern of pancreatitis reported in three dulaglutide-treated patients with acute or indeterminate type. All events of acute pancreatitis occurred in patients treated with doses equal to or lower than the highest approved dulaglutide dose of 1.5 mg. No patient who received higher doses in these nine studies had pancreatitis. It is noteworthy that all three patients had elevations in pancreatic enzyme levels prior to exposure, which may indicate the presence of preexisting abnormalities. One of these patients had gallbladder stones, a major risk factor for acute pancreatitis (32). It is also important to note that two of the five cases of pancreatitis confirmed by adjudication in dulaglutide-treated patients were classified as chronic pancreatitis, a condition that seems unlikely to be causally related to treatment with dulaglutide because of the short period of exposure to the drug.

The results for acute pancreatitis described in this report are further supported by the assessment of the entire database to search for cases that did not meet the criteria for this condition, but presented with additional nondiagnostic clinical findings (Table 3). Overall, these events led to an appropriate workup with respect to pain characteristics, the availability of pancreatic enzymes, and the use of imaging procedures, which, however, did not provide enough evidence to confirm pancreatitis. We can only speculate whether some of these patients may have had subclinical pancreatitis. On the other hand, a majority of these patients had elevations in enzyme levels prior to randomization, suggesting a possibility that the preexisting enzyme abnormalities in patients with treatment-emergent gastrointestinal symptoms unrelated to the pancreas may lead to a false clinical diagnosis of "mild pancreatitis." Nevertheless, a small number of such cases was similarly distributed across the major treatment groups, those groups exposed to dulaglutide and those exposed to nonincretin comparators. Overall, the findings from our report are consistent with data from animal studies of dulaglutide, which did not yield any relevant dulaglutide-related histological effects on the exocrine pancreas (33).

Based on regulatory input provided in 2008 and 2009, the dulaglutide development program included serial measurements of pancreatic enzymes as a standard procedure for all enrolled patients. The main purpose was to capture potential subclinical events based on the presence of clinically relevant increases in these enzymes (≥3× ULN). There were no cases of patients having treatment-emergent elevations in pancreatic enzyme levels, in

the absence of other signs or symptoms, that later evolved to acute pancreatitis. The overall experience with using these laboratory tests to screen for preexisting subclinical changes suggested limited clinical value in the detection of patients' increased risk for acute pancreatitis. In addition, when evaluating the utility of this diagnostic strategy, it is also important to take into account its adverse effects on medical safety (e.g., abdominal imaging, repeated blood draws, emotional stress) and the costs induced.

We have observed an increased concentration of pancreatic enzymes, above the ULN, in many patients prior to exposure to randomized therapies. This finding, which has been recently reported by several other groups (34,35), suggests an association between pancreatic hyperenzymemia and type 2 diabetes. In addition, we are reporting mild, chronic, reversible time-dependent elevations in pancreatic enzymes upon exposure to dulaglutide (11–21% from baseline values), exenatide, and sitagliptin. Similarly, in AWARD-6 liraglutide was associated with an increase in the level of pancreatic enzymes that was greater than with dulaglutide 1.5 mg dose (20). In AWARD-3, which compared dulaglutide monotherapy to treatment with metformin, an increase in the median concentration of enzymes was also observed with metformin; however, the absence of a placebo arm in this trial precludes a reliable conclusion on the effects of metformin. Notably, the elevations in patients who received dulaglutide tended to return to near-baseline levels at the end of the 4-week safety follow-up, during which the patients were off their medications. Similar results have been recently reported by others (36). We cannot provide a clear explanation for these changes. In multiple analyses (data not included), we did not observe differences based on baseline pancreatic enzyme status or based on kidney function in the incidence of patients shifting upward from one category to the next. As discussed above, we can suggest that chronic stimulation of the GLP-1 receptor by increased concentration of exogenous or endogenous ligand enhances the release of digestive enzymes from the acinar cells. This interaction may also include the parasympathetic part of the autonomic nervous system through its role in the regulation of exocrine pancreas secretion that can be modulated by incretins via GLP-1 receptors expressed in some section of the system (3,37). Another hypothesis is that the GLP-1–mediated increase in pancreatic mass, which has been shown in some animal models (38,39), increases the amount of pancreatic enzymes that are available for release into the systemic circulation. Hyperenzymemia may also be a marker of a physiological adjustment to the changes initiated by the actions of randomized therapies, for example, changes in upper gastrointestinal motility or changes in food intake or body weight. This adjustment may involve changes in the physiological gastroenteropancreatic signaling. An elevation in pancreatic enzyme levels with sitagliptin as in AWARD-5 has not been reported previously. A mechanism needs to be delineated (40).

An important limitation of the assessments presented in this report was the sample size, which was not large enough to definitively characterize the risk of acute pancreatitis with the various antidiabetic treatments studied in the dulaglutide development program. The duration of exposure, at least in some of the included trials, may have been too short for a definitive conclusion on the effects of long-term exposure to various treatments on the exocrine pancreas.

In conclusion, data from nine phase 2 and phase 3 trials do not suggest an increased risk of acute pancreatitis in patients treated with dulaglutide, a once-weekly GLP-1 receptor agonist. The use of repeated measurements of pancreatic enzymes has limited clinical value in routine testing in asymptomatic patients for predicting episodes of acute pancreatitis.

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